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# Perceptual inference and learning in autism : a behavioral and neurophysiological approach

Laurie-Anne Sapey-Triomphe

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**Laurie-Anne Sapey-Triomphe**

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# Inférence et apprentissage perceptifs dans l'autisme : une approche comportementale et neurophysiologique

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Perceptual inference and learning in autism:  
a behavioral and neurophysiological approach

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## RESUME

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Les troubles du spectre de l'autisme (TSA) sont caractérisés par des difficultés dans les interactions sociales, des intérêts restreints, et une perception sensorielle atypique. Il a été proposé récemment que ces symptômes puissent être liés à un défaut d'inférence et d'apprentissage Bayésien ; des processus qui reposent sur le poids relatif accordé aux entrées sensorielles et aux prédictions. Cette théorie est prometteuse pour le diagnostic et la prise en charge psychiatriques. Cependant, les preuves expérimentales en sa faveur demeurent parcimonieuses.

Cette thèse a pour objectif une meilleure caractérisation de la sensorialité, de l'inférence perceptive et de l'apprentissage dans les TSA. Pour cela, nous avons utilisé des questionnaires, des mesures comportementales, des modèles computationnels, ainsi que de l'imagerie et de la spectroscopie par résonance magnétique auprès d'adultes avec ou sans TSA.

Les profils sensoriels des personnes avec hauts quotients autistiques ont été affinés grâce à un questionnaire dont nous avons validé la version française. Nous avons ensuite montré que les personnes avec TSA étaient moins enclines à utiliser spontanément un type d'apprentissage permettant de généraliser. Puis à l'aide d'une tâche de discrimination tactile, nous avons montré que les sujets avec TSA pouvaient implicitement apprendre la régularité des stimulations, mais ajustaient difficilement leurs croyances au contexte. Enfin, des résultats préliminaires portant sur les corrélats neurophysiologiques de l'inférence perceptive suggèrent un réseau cérébral distinct et une neuromodulation différente dans les TSA, par rapport aux contrôles.

Ces résultats, obtenus à plusieurs échelles, confirment un possible déficit de l'apprentissage perceptif qui pourrait être central dans les TSA. Ils appellent désormais au développement de modèles génératifs permettant la caractérisation et la quantification au niveau individuel des TSA.

***Mots clés:** Troubles du spectre de l'autisme ; inférence perceptive ; apprentissage ; cerveau Bayésien ; a priori ; erreur de prédiction ; sensibilité sensorielle ; imagerie et spectroscopie par résonance magnétique*

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## ABSTRACT

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Autism spectrum disorders (ASD) are characterized by difficulties in social interactions, restricted interests and atypical sensory perception. Recently, it has been suggested that most ASD symptoms could result from a failure to implement Bayesian inference and learning. At the heart of this process is the relative weight given to sensory inputs and descending predictions. Beyond ASD, such theories are very promising in enabling new, individual and quantitative approaches to improve diagnosis and therapies in psychiatry. However, empirical evidence from studies designed to test and refine these hypotheses remain scarce.

This thesis aimed at better characterizing sensory sensitivity, perceptual inference and learning in ASD, using first-person questionnaires, behavioral measures, computational models and magnetic resonance imaging and spectroscopy in adults with or without ASD.

Sensory profiles in people with high autism spectrum quotients were refined, using a questionnaire that we validated in French. We then evidenced that subjects with ASD were less inclined to spontaneously use a learning style enabling generalization in a visual task. A two-alternative forced choice tactile task further showed that subjects with ASD could learn implicit regularities but were inflexible in adjusting their belief to the context. Finally, preliminary results in the investigation of the neurophysiological correlates of perceptual inference suggest a distinct neural network and neuromodulation in ASD, compared to controls.

These multilevel results tend to confirm the possible core impairment of perceptual learning in ASD. They also call for further developments in computational approaches to be more task, context and individual specific as well as to draw more quantitative conclusions in relating the behavioural, neuronal and molecular levels. Such conclusions may considerably improve our fundamental and clinical approach to ASD.

**Keywords:** *Autism spectrum disorders; Sensory sensitivity; Perception; Learning; Bayesian inference; Predictive coding; magnetic resonance imaging and spectroscopy*

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*Alors que les différences nous inquiètent,  
pourquoi ne pas les transformer en force pour  
nous mener plus loin dans nos échanges, le  
plus naturellement possible, et partager notre  
authenticité en toute modestie ?*

Albert Jacquard

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## LIST OF ACRONYMES

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**ACC:** Anterior cingulate cortex  
**Ach:** Acetylcholine  
**AQ:** Autism-spectrum quotient  
**ASD:** Autism spectrum disorder  
**BMA:** Bayesian model averaging  
**BMS:** Bayesian model selection  
**BOLD:** Blood-oxygen-level dependent imaging  
**DSM:** Diagnosis and Statistical Manual of mental disorders  
**EEG:** Electroencephalography  
**GABA:** Gamma-aminobutyric acid  
**GSQ:** Glasgow sensory questionnaire  
**HIPPEA:** High and inflexible precision of prediction error in autism  
**IFG:** Inferior frontal gyrus  
**INT:** Interpolation learning style  
**IPL:** Inferior parietal lobe  
**LUT:** Lookup table learning style  
**MEG:** Magnetoencephalography  
**MMN:** Mismatch negativity  
**MNS:** Mirror neuron system  
**MRI:** Magnetic resonance imaging  
**MRS:** Magnetic resonance spectroscopy  
**NE:** Norepinephrine  
**NT:** Neurotypical  
**OFC:** Orbitofrontal cortex  
**PE:** Prediction error  
**PET:** Positron emission tomography  
**PFC:** Prefrontal cortex  
**S1:** Primary somatosensory cortex  
**S2:** Secondary somatosensory cortex  
**TOE:** Time-order effect  
**ToM:** Theory of mind  
**WCC:** Weak central coherence

*NB: These acronyms are always first defined in the text before being used as abbreviations.*



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## MATHEMATICAL NOTATIONS

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### *Main notations in the introduction*

<b>Notation</b>	<b>Meaning</b>
$\propto$	proportional to
$\mathbf{x}$	mean
$\mathbf{v}$	variance
$\boldsymbol{\pi}$	precision

### *Main notations in the computational models (Study III)*

<b>Notation</b>	<b>Meaning</b>
$\mathbf{s}$	Sensory stimulation
$(\mathbf{s1}, \mathbf{s2})$	(1 <sup>st</sup> , 2 <sup>nd</sup> stimulation)
$\boldsymbol{\theta}$	Sensory stimulation mean
$\boldsymbol{\pi}_s$	Sensory stimulation precision
$\boldsymbol{\theta}_0$	Prior mean
$\boldsymbol{\pi}_\theta$	Prior precision
$r$	Prior to sensory stimulation ratio
$\boldsymbol{\mu}$	Percept mean
$\boldsymbol{\pi}_{\theta s}$	Percept precision



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# THEORETICAL BACKGROUND

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# I. Autism Spectrum Disorder characterization

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## ***I. 1. Clinical description of ASD***

### *I. 1. A. History*

The term *autism* comes from the Greek word *autos*, which means *oneself*. The term first appeared in 1911, when the Swiss psychiatrist Eugène Bleuler described in schizophrenic patients symptoms of self-absorption that impaired communication (Bleuler, 1930). Later, in 1943, the Austrian-American child psychiatrist Léo Kanner introduced the label *early infantile autism* in his seminal article untitled *Autistic Disturbance of Affective Contact* (Kanner 1943). As opposed to Bleuler who characterized autism as a symptom of schizophrenia, Kanner used the word *autism* to describe an independent clinical syndrome, already present at birth. He defined autism based on the observation of eleven cases of children, and explained that in autism, “*the outstanding, ‘pathognomonic’ fundamental disorder is the children’s inability to relate themselves in the ordinary way to people and situations from the beginning of life*” (Kanner 1943). Kanner had noted particularities in the behavior of these children, such as atypical social interactions, insistence on uniformity, hyper- or hypo-reactivity to sensory stimuli, unusual learning, impaired language production and comprehension, stereotypies (repetitive movement or utterance) and impaired motor adjustment.

Independently, in 1944, the Austrian pediatrician Hans Asperger described the *autistic psychopathology* (Asperger 1944). Asperger had been working on case studies of four boys, who were “*very unchildlike children*” (Frith 1991). His work remained relatively unknown for a couple of decades, before Lorna Wing introduced the notion of “*Asperger syndrome*” in 1981 (Wing 1981), and Uta Frith translated his article in 1991 (Frith 1991). Asperger described children with normal intelligence and no language delay, but who presented with a pattern of behaviors that he called “*autistic psychopathy*”, such as intense absorption in a special interest and impaired social communication. Asperger documented both positive and negative features of this symptom. He called these children “*little professors*” as they could provide lots of details on their topic of special interest.

In their pioneering articles, Kanner and Asperger both described autism as a developmental disorder and set the basis for autistic symptoms characterization. Of particular interest are the comments made by Kanner and Asperger on sensory sensitivity, learning and unexpectedness in autism.

The first case described by Kanner was a young boy named Donald, who reported abnormal sensory sensitivity: *“Another intrusion comes from loud noises and moving objects, which are therefore reacted with horror”*. This child demonstrated hyper responsiveness to sensory stimulations: for instance, *“he was perfectly petrified of the vacuum cleaner”*. Kanner assumed that these unusual sensory reactions were caused by the disruption of the child solitude, rather than by general sensitivity abnormalities: *“Direct physical contact or such motion or noise as threatens to disrupt the aloneness is either treated as if it weren’t there, or [...] resented painfully as distressing interference”* (Kanner, 1943).

In addition, atypical learning was described: *“He had an unusual memory for faces and names, knew the names of a great number of houses”*, but despite his good memory, *“He seemed unable to generalize, transfer an expression to another similar object”* (Kanner, 1943). He noticed that the excellent memory of these children *“often led the parents to stuff them with more and more verses, zoological and botanic names”* (Kanner, 1943). Hence, these children presented with an atypical learning as they were able to memorize a great number of specific items, but failed to generate generalizable rules.

Besides, Kanner and Asperger both noted that children with autism had difficulties to deal with novelty. Kanner noticed that unexpected changes greatly disturbed children with autism: *“He became upset by any change of an accustomed pattern: if he notices change, he is very fussy and cries”* (Kanner, 1943). The daily activities needed to be strictly planned and without any change from one day to another: *“All these and many other things were not only repetitions but recurred day after day with almost photographic sameness”* (Kanner, 1943). This need for consistency was also reported by Asperger who explained that *“the children [...] may inadvertently tyrannize their family by intolerance of any change in routine”*. Kanner interpreted it as a need for experiences to be lived precisely in the same way as they had been first experienced: *“Their world must seem to them to be made of elements that, once they have been experienced in a certain setting or sequence, cannot be tolerated without all the original ingredients in the identical spatial or chronological order”* (Kanner, 1943).

### *I. 1. B. Autism spectrum disorder diagnosis*

During the two last decades, the Diagnosis and Statistical Manual of mental disorders IV (DSM-IV) characterized autism with a triad of symptoms: impaired social interactions, impaired communication, as well as restrictive and repetitive behaviors.

In 2013, a new version of the DSM (DSM-5, American Psychiatric Association 2013) was released that now defines autism as a spectrum: Autism Spectrum Disorders (ASD). Noticeably, the notion of spectrum had already been suggested in 1979 (Wing and Gould 1979). The definition of autism as a spectrum highlights the fact that there are several degrees of symptom severity, a continuum in the social abilities impairments, diverse manifestations of the disorder and a possible evolution of the symptoms throughout life. In the DSM-5, ASD is now defined as a neurodevelopmental disorder, characterized by two core domains: impairments in social interactions and communication, and restrictive and repetitive patterns of behaviors, interests and activities. The DSM-5 criteria for ASD diagnosis are listed in Table 1. With the DSM-5, ASD can be diagnosed with 3 levels of severity assessed by the amount of support needed by the patient.

Interestingly, a new sub-criterion for ASD appeared in the DSM-5, which takes into account sensorial abnormalities “*Hyper- or hypo-reactivity to sensory input or unusual interests in sensory aspects of the environment*”. Rather than being another piece of the puzzle, atypical sensory perception in ASD could be a core symptom leading to higher cognitive level impairments (Baum et al. 2015).

The notion of ASD now encompasses the subgroups previously defined in the DSM-IV: autism, Asperger syndrome, childhood disintegrative disorder and pervasive developmental disorder not otherwise specified. ASD individuals can be described as having or not intellectual deficiency and language delay. Asperger syndrome and high-functioning autism are now referred to ASD without intellectual deficiency for both groups, and without language delay for Asperger syndrome. Even though these terms officially disappeared, many of the individuals diagnosed with Asperger syndrome keep referring to themselves as “Asperger” or “Aspies”.

In this thesis, every participant involved in the experiments was diagnosed before 2013 and did not present with any intellectual deficiency (i.e. Asperger syndrome or high-functioning autism, according to the DSM-IV).

**Table 1: Diagnostic Criteria for Autism Spectrum Disorders**  
(American Psychiatric Association 2013)

**Persistent deficits in social communication and social interactions across multiple contexts,** as manifested by the following, currently or by history:

1. Deficits in social-emotional reciprocity, ranging, for example, from abnormal social approach and failure of normal back-and-forth conversation; to reduced sharing of interests, emotions, or affect; to failure to initiate or respond to social interactions.
2. Deficits in nonverbal communicative behaviors used for social interaction, ranging, for example, from poorly integrated verbal and nonverbal communication; to abnormalities in eye contact and body language or deficits in understanding and use of gestures; to a total lack of facial expressions and nonverbal communication.
3. Deficits in developing, maintaining, and understanding relationships, ranging, for example, from difficulties adjusting behavior to suit various social contexts; to difficulties in sharing imaginative play or in making friends; to absence of interest in peers.

**Restricted, repetitive patterns of behaviors, interests, or activities,** as manifested by at least two of the following, currently or by history:

1. Stereotyped or repetitive motor movements, use of objects, or speech.
2. Insistence on sameness, inflexible adherence to routines, or ritualized patterns or verbal nonverbal behavior.
3. Highly restricted and fixated interests that are abnormal in intensity or focus.
4. Hyper- or hypo-reactivity to sensory input or unusual interests in sensory aspects of the environment.

**Symptoms must be present in the early developmental period** (but may not become fully manifest until social demands exceed limited capacities, or may be masked by learned strategies in later life).

**Symptoms cause clinically significant impairment** in social, occupational, or other important areas of current functioning.

**These disturbances are not better explained by intellectual disability or global developmental delay.** Intellectual disability and ASD frequently co-occur; to make comorbid diagnoses of ASD and intellectual disability, social communication should be below that expected for general developmental level.

In ASD, autistic symptoms are present before the age of 3, but are often diagnosed later, especially for individuals with Asperger syndrome. Among Medicaid-enrolled children, the mean age for ASD diagnosis was 5 years old (Mandell et al. 2010). In general, diagnosis cannot be reliably made before the age of 2 to 3 years old, even if some studies attempted to identify earlier signs for ASD (Pierce et al. 2009; Georgiades et al. 2013; Herlihy et al. 2015;

Zwaigenbaum et al. 2015). Several tools were developed to screen for these symptoms in infants, children, adolescents and adults, as shown in Table 2.

Haker et al. (2016) highlighted four clinical challenges that should be resolved to help diagnosing ASD: finding quick and easy tests facilitating diagnosis, diagnosing mild forms of ASD, diagnosing very young children at risk of ASD, and assessing intelligence in ASD patients without spoken language.

**Table 2 : Screening instruments for ASD diagnosis**  
(Lai et al. 2014)

	Age	Description
<b>Screening: young children</b>		
Checklist for autism in toddlers (CHAT)	18 months	14-item questionnaire: nine completed by parent or caregiver and five by primary health-care provider; takes 5–10 min
Early screening of autistic traits (ESAT)	14 months	14-item questionnaire: completed by health practitioners at well-baby visit after interviewing parent or caregiver; takes 5–10 min
Modified checklist for autism in toddlers (M-CHAT)	16–30 months	23-item questionnaire: completed by parent or caregiver; takes 5–10 min
Infant toddler checklist (ITC)	6–24 months	24-item questionnaire: completed by parent or caregiver; takes 5–10 min
Quantitative checklist for autism in toddlers (Q-CHAT)	18–24 months	25-item questionnaire: completed by parent or caregiver; takes 5–10 min; ten-item short version available
Screening tool for autism in children aged 2 years (STAT)	24–36 months	12 items and activities: assessed by clinician or researcher after interacting with the child; takes 20 min; intensive training necessary; level-two screening measure
<b>Screening: older children and adolescents</b>		
Social communication questionnaire (SCQ)	>4 years (and mental age >2 years)	40-item questionnaire: completed by parent or caregiver; takes 10–15 min
Social responsiveness scale, first or second edition (SRS, SRS-2)	>2.5 years	65-item questionnaire: completed by parent, caregiver, teacher, relative, or friends (self-report form available for adult in SRS-2); takes 15–20 min
Childhood autism screening test (CAST)	4–11 years	37-item questionnaire: completed by parent or caregiver; takes 10–15 min
Autism spectrum screening questionnaire (ASSQ)*	7–16 years	27-item questionnaire: completed by parent, caregiver, or teacher; takes 10 min
Autism spectrum quotient (AQ), child and adolescent versions*	Child: 4–11 years; adolescent: 10–16 years	50-item questionnaire: completed by parent or caregiver; takes 10–15 min; ten-item short versions available
<b>Screening: adults</b>		
Autism spectrum quotient (AQ), adult version*	>16 years (with average or above-average intelligence)	50-item questionnaire: self-report; takes 10–15 min; ten-item short version available
The Ritvo autism Asperger diagnostic scale-revised (RAADS-R)	>18 years (with average or above-average intelligence)	80-item questionnaire: self-report; done with a clinician; takes 60 min
<b>Diagnosis: structured interview</b>		
The autism diagnostic interview-revised (ADI-R)	Mental age >2 years	93-item interview of parent or caregiver; takes 1.5–3 h; intensive training necessary
The diagnostic interview for social and communication disorders (DISCO)	All chronological and mental ages	362-item interview of parent or caregiver; takes 2–4 h; intensive training necessary
The developmental, dimensional, and diagnostic interview (3Di)	>2 years	266-item computer-assisted interview of parent or caregiver; takes 2 h; 53-item short form available, which takes 45 min; intensive training necessary
<b>Diagnosis: observational measure</b>		
The autism diagnostic observation schedule, first or second edition (ADOS, ADOS-2)	>12 months	Clinical observation via interaction: select one from five available modules according to expressive language level and chronological age; takes 40–60 min; intensive training necessary
Childhood autism rating scale, first or second edition (CARS, CARS-2)	>2 years	15-item rating scale: completed by clinician or researcher; takes 20–30 min; accompanied by a questionnaire done by parent or caregiver; moderate training necessary
For version with full references and for sources, see appendix. *Particularly sensitive for high-functioning individuals.		
<b>Table 3: Screening and diagnostic instruments</b>		



### *I. 1. C. Autism plus*

Gillberg suggested to use the term *Autism Plus* to refer to ASD with comorbidities, as other troubles, such as intellectual developmental disorder or language disorders, frequently occur in ASD (Gillberg and Fernell 2014). As mentioned by Gillberg, “*Autism is but one of the Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examination (ESSENCE), not the one and only*”. Interestingly, children under four years old are more likely to be diagnosed with ASD if they have a form of *Autism Plus* rather than *Autism Only* (Carlsson et al. 2013).

Multiple comorbidities were reported in ASD, including intellectual developmental disorder, language disorder, attention deficit and hyperactivity disorder (ADHD), tics, obsessive compulsive behaviors, sleep disorders or eating disorders (Leyfer et al. 2006; Carlsson et al. 2013; McCary and Roberts 2013; Eapen et al. 2016). For instance, over 30% of children with ASD would meet criteria for ADHD, and children with this comorbidity would have higher autistic traits and exacerbated impairments in executive control and adaptive behaviors (Leyfer et al. 2006; Yerys et al. 2009). A list of frequent comorbidities reported in ASD is shown in Table 3.

A high proportion of individuals with ASD experience depression and anxiety disorders. Indeed, half of the ASD population suffers from anxiety disorders (Lugnegård et al. 2011). Furthermore, depressive symptoms were described in children, adolescents, and adults with ASD, and it is estimated that 70% of the adults with ASD have experienced at least one episode of major depression (Lugnegård et al. 2011; Magnuson and Constantino 2011; Gotham et al. 2015). Finally, the comorbidity with intellectual deficiency would range between 12 and 70% in ASD (Lai et al. 2014).

The two core symptoms characterizing ASD might not always be the most inconvenient, as additional troubles might be handicapping and requiring increased need for assistance. The ESSENCE project is currently investigating the continuum between several neurodevelopmental disorders (Gillberg and Fernell 2014), as they suggest that ASD might not only appear as a spectrum, but also as a continuum with many other psychiatric, psychologic and medical disorders.

**Table 3 : List of comorbidities in ASD (Lai et al. 2014)**

<b>Developmental</b>	
Intellectual disability	45 %
Language disorders	Variable
Attention-deficit hyperactivity disorder	28-44 %
Tic disorders	14-38 %
Motor abnormality	≤79 %
<b>General medical</b>	
Epilepsy	8-30 %
Gastrointestinal problems	9-70 %
Immune dysregulation	≤38 %
Genetic syndromes	~5 %
Sleep disorders	50-80 %
<b>Psychiatric</b>	
Anxiety	42-56 %
Depression	12-70 %
Obsessive-compulsive disorder	7-24 %
Psychotic disorders	12-17 %
Substance use disorders	≤16 %
Oppositional defiant disorder	16-28 %
Eating disorders	4-5 %

From the first description of ASD to current research projects, the characterization of ASD keeps on refining. Figure 1 summarizes the part I.1.



**Figure 1 : Summary of part I.1**

## I.1. Clinical description of ASD

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First descriptions of autism:

- Early infantile autism by Léo Kanner (1943)
- Asperger syndrome by Hans Asperger (1944)

L. Kanner      H. Asperger

Autism Spectrum Disorder (ASD)

Deficits in social communication and social interactions

Restricted, repetitive patterns of behaviors, interests or activities

- ▷ Symptoms present in the early developmental period
- ▷ Notion of sensory abnormalities in ASD: new in the DSM-5
- ▷ Notion of *Autism Plus* to take into account the frequent comorbidities.

## ***1.2. Epidemiology and etiology of ASD***

### ***1.2.A. Epidemiology of ASD***

ASD prevalence estimation has been evolving significantly over the past decades. Estimated to 1 birth out of 2500 in the early 70s, and then to 1 birth out of 250 in the early 2000s (Fombonne 2003a; Yeargin-Allsopp et al. 2003), ASD prevalence has recently dropped to 1 birth out of 68 in 8-year-old American children (Christensen et al. 2016a). Interestingly, the prevalence in 4-year-old children was 13 births out of 1000, which is 30% lower than the prevalence found in 8-years-old (Christensen et al. 2016b). This difference suggests that early diagnoses are probably still suboptimal in young children, and highlights the need for earlier detection. The average prevalence for ASD ranged from 1 to 2% in studies performed in Asia, Europe and North America (Christensen et al. 2016a). Asperger syndrome prevalence ranges from 2 to 56 cases out of 10000 (Fombonne 2003b; Ishikawa and Ichihashi 2007).

Changes in practices for diagnosing ASD partially explain this increased prevalence (King and Bearman 2009; Hansen et al. 2015). The definition of ASD became broader with changes in the DSM-4, and in particular, in the DSM-5. Re-categorization of cases with ASD diagnosis would explain 59% of the increase in prevalence in 8-year-old children, and 97% in the 15-year-old adolescents (Polyak et al. 2015).

Remarkably, ASD is 4.5 times more common in boys than girls, as ASD prevalence is 1 in 42 boys, against 1 in 189 girls (Christensen et al. 2016a). However, in the case of individuals with ASD and profound cognitive impairments, the male-female ratio drops to 1.3 (Yeargin-Allsopp et al. 2003).

### ***1.2.B. A genetic background of ASD***

The very first descriptions of autism already suggested that ASD was innate and that it could be genetically transmitted (Kanner 1943; Asperger 1944; Frith 1991). In their pioneering genetic study of ASD, Folstein and Rutter (1977) investigated the occurrence of autism in same-sex monozygotic or dizygotic pairs of twins. They found that ASD diagnosis was given to 2 twins in 4 pairs out of the 11 monozygotic twins studied, whereas it never happened in the 10 other dizygotic twins. A decade later, concordance for autism in monozygotic pairs of twins was estimated to 91% (Steffenburg et al. 1989).

The unbalanced sex ratio observed in ASD has driven some of the first genetic studies to investigate the possible involvement of the X chromosome in ASD, which revealed chromosomal abnormalities (Rao et al. 1994; Thomas et al. 1999). Polymorphisms in the reelin gene (*RELN*) associated with vulnerability to ASD, and deletions in the neuroligin genes (*NLGN3*, *NLGN4*) in subjects with ASD were then identified (Persico et al. 2001; Jamain et al. 2003). These results were suggestive of an abnormal brain development in ASD.

A genetic cause could be determined in 25% of individuals with ASD (Delorme et al. 2013; Huguet et al. 2013). Chromosomal rearrangements and rare copy number variants would be found in 10 to 20% of people with ASD, while *de novo* mutations in coding sequences would be found in 5 to 10% of people with ASD (Huguet et al. 2013). Most of the genes identified in ASD are involved in pathways that might alter synaptic homeostasis. Copy number variations and mutations are frequently reported in glutamatergic and GABAergic synapses genes, which are involved in synaptogenesis, neuronal functions and long term potentiation (Autism Genome Project Consortium et al. 2007; Delorme et al. 2013). More than 200 genes could be involved in ASD, and only the main ones will be succinctly addressed here.

Mutations in *SHANK2* and *SHANK3* seem to be the most frequent in ASD, even though only 1 to 2% of individuals with ASD would carry one of these mutations (Durand et al. 2007; Leblond et al. 2012). SHANK proteins are located in the post-synaptic density of glutamatergic synapses and are important for neuronal functioning and synaptic homeostasis. In addition to mutations in *NLGN*, mutations were found in the gene coding for neurexin (*NRXN*) (Kim et al. 2008). *NRXN* is a presynaptic membrane protein which interacts with *NLGN* in glutamatergic and GABAergic synapses. These mutations reinforce the idea of an impaired synaptogenesis in ASD.

Not only glutamate/GABA synapses seem to be affected in ASD (with *NLGN*, *NRXN* or *SHANK*), but also cholinergic synapses. A study investigating three ASD individuals with *de novo* deletion of *SHANK2* revealed copy number variations including genes involved in the cholinergic nicotinic receptors (Leblond et al. 2012). Furthermore, a cholinergic muscarinic deletion was reported in ASD (Petersen et al. 2013). The cholinergic and glutamatergic systems play a central role in learning.

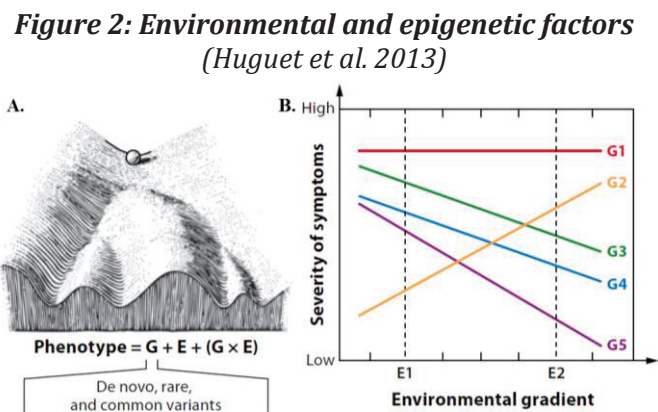
In conclusion, ASD would be caused by a complex set of heterogeneous risk factors that would influence common pathways involved in neuronal and synaptic homeostasis (Pinto et al. 2010, 2014; Leblond et al. 2012; Huguet et al. 2013). Together with genetic predisposition, epigenetic and environmental factors would lead to ASD development.

### I. 2. C. Impact of epigenetic and environmental factors in ASD

As genetics alone do not account for every case of ASD, epigenetic and environmental factors might contribute to ASD (Hallmayer 2011) (Figure 2). ASD would be polygenic and epistatic, and environmental factors would increase ASD risk (Carter et al. 2016; Vijayakumar et al. 2016). The *epiphenomenon hypothesis* argues for a primary role of genetic factors, and suggests that these genetic factors would increase risks for prenatal and postnatal complications (Glasson et al. 2004). The *heterogeneity hypothesis* suggests that the relative contribution of genetic and environmental factors varies among individuals with ASD (Tordjman et al. 2014). The effects of environmental factors would depend on the developmental window. Gene variations and environmental factors would often lead to increased brain oxidative stress in ASD (Tordjman et al. 2014).

Prenatal exposure to several toxins would increase the risks of ASD. ASD risk factors include exposure to thalidomide, to valproic acid or to misoprostal during the first trimester of pregnancy, viral and bacterial infections during the two first trimesters, and stress and vitamin D deficiency in the third trimester (see Dietert et al. 2011 for a review). Prenatal exposure to organophosphate insecticides, pesticides or air pollution would also be linked to increased ASD risk (Landrigan 2010; De Felice et al. 2016; Sealey et al. 2016). Other physical stress such fetal distress, birth injury, trauma or neonatal anemia might contribute to increased risk of ASD (Gardener et al. 2011). However, meta-analyses were not able to incriminate only one perinatal or one neonatal factor that could explain ASD etiology (Gardener et al. 2011).

Interactions between genetic and environmental factors are mediated by epigenetics (i.e. modulation of gene expression through DNA cytosine methylation and histone<sup>1</sup> modifications). Usually, these modifications are



<sup>1</sup> Histones are proteins packaging DNA into units called nucleosomes. The more condensed the DNA is (with histones and other proteins), the less gene transcription is made. Post-translational modifications of histones can modulate gene expression level (e.g. histone acetylation usually leads to increased gene expression).

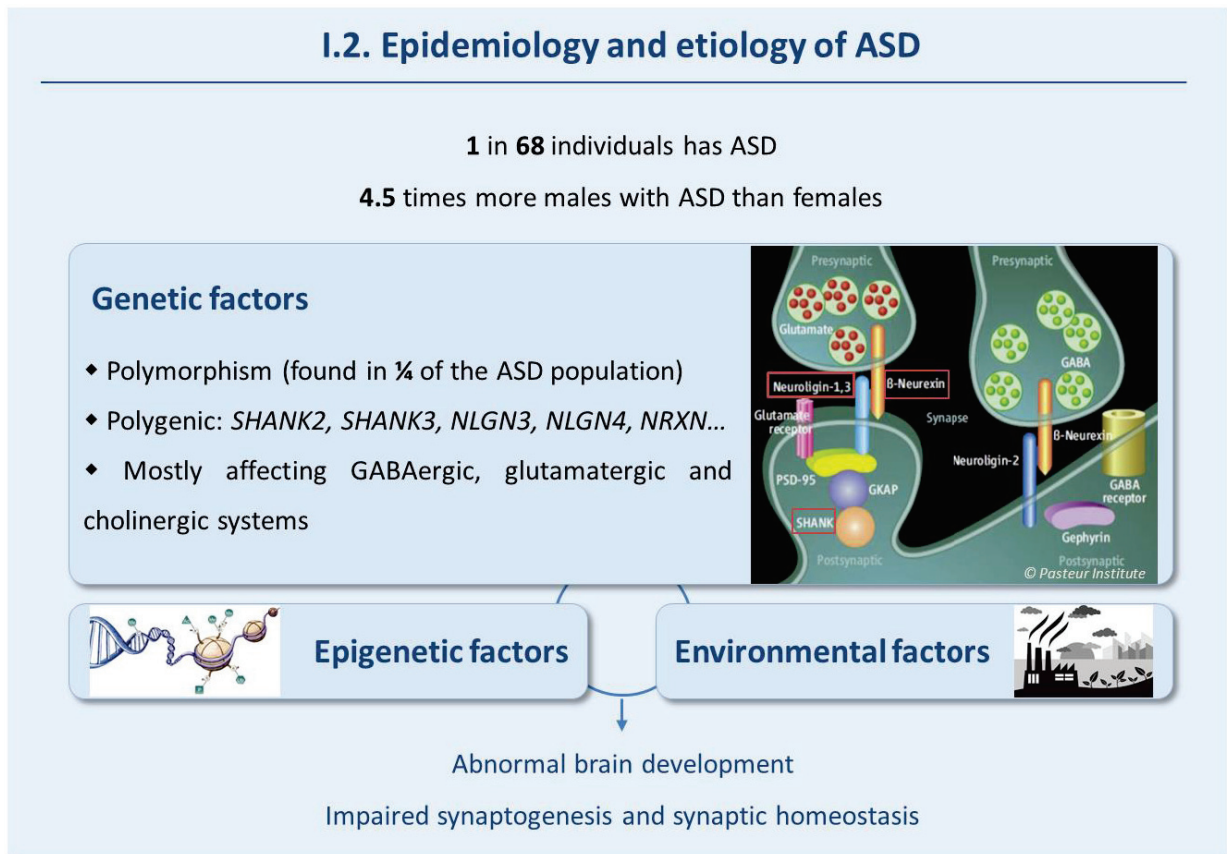
reversible, even though DNA methylation appears to be more stable than histone modification. Importantly, epigenetic modifications can be transmitted across generations (Franklin et al. 2010). Differential DNA methylation can affect synaptic plasticity and neuronal excitability (Oh et al. 2013). A few post-mortem studies on ASD suggest epigenetic modifications in ASD (James et al. 2013).

Interestingly, prenatal air pollution and valproate exposure would lead to epigenetic modifications, which would affect brain structure and function (Tordjman et al. 2014). Many rodent models of ASD use valproate administration during prenatal life, as it leads to the emergence of autistic behaviors (Chapman and Cutler 1989; Markram et al. 2007; Markram and Markram 2010).

In conclusion, ASD development would result from complex interactions between multiple genetic variations or mutations, environmental factors and epigenetics, in specific developmental critical windows. Gene expression has a major importance to control the principle steps of brain development.

Results on epidemiology and etiology of ASD are summarized in Figure 3.

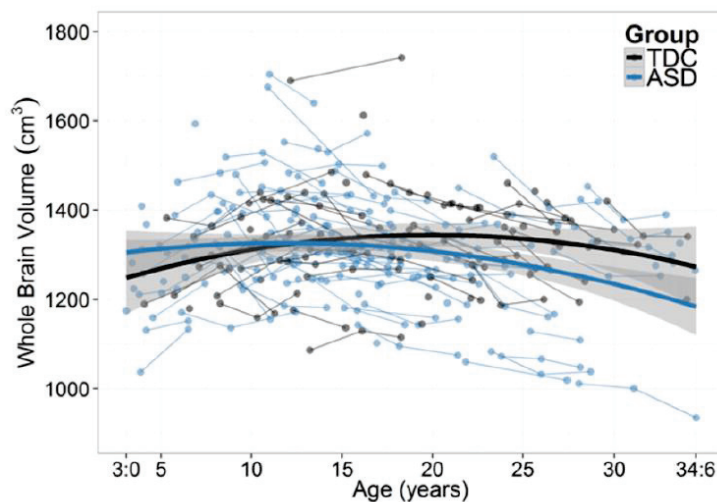
**Figure 3 : Summary of part I.2**



### ***I. 3. Neurophysiological correlates of ASD***

#### ***I. 3. A. Brain developmental patterns in ASD***

Several studies based on head circumference measurements suggest that brain growth is abnormal in ASD (Courchesne 2003; Courchesne et al. 2007; Amaral et al. 2008). The evolution of brain volume during development is illustrated in Figure 4. In individuals with ASD, the head circumference would be reduced at birth, and would be followed by a sudden increased growth between 1 to 2 months and 6 to 14 months (Courchesne 2003; Dementieva et al. 2005). The early overgrowth would correspond to a 10% increase in brain volume (Anagnostou and Taylor 2011). The brain development rate would then decelerate and plateau during the second year of life, where the symptoms start to increase (Redcay and Courchesne 2005; Dawson et al. 2007). Five to 10% of the children with ASD aged between 18 months and 4 years, would have abnormal enlargement in total brain volume (Amaral et al. 2008), but it is unclear whether this enlargement remains later. fMRI and DTI studies show that these brain volume abnormalities would be linked with atypical structural and functional connectivity in ASD (Anagnostou and Taylor 2011).



**Figure 4 : Evolution of brain volume with age**  
(Lange et al. 2015)

*Correlation between whole brain volume and age for ASD and TDC individuals*

*ASD: autism spectrum disorder,  
TDC: typically developing control*

The brain enlargement would be mostly due to an increase in the white matter (Courchesne et al. 2001; Hazlett et al. 2005). Cortical thickness would globally increase in adults, but findings remain heterogeneous (Bailey et al. 1998; Amaral et al. 2008).

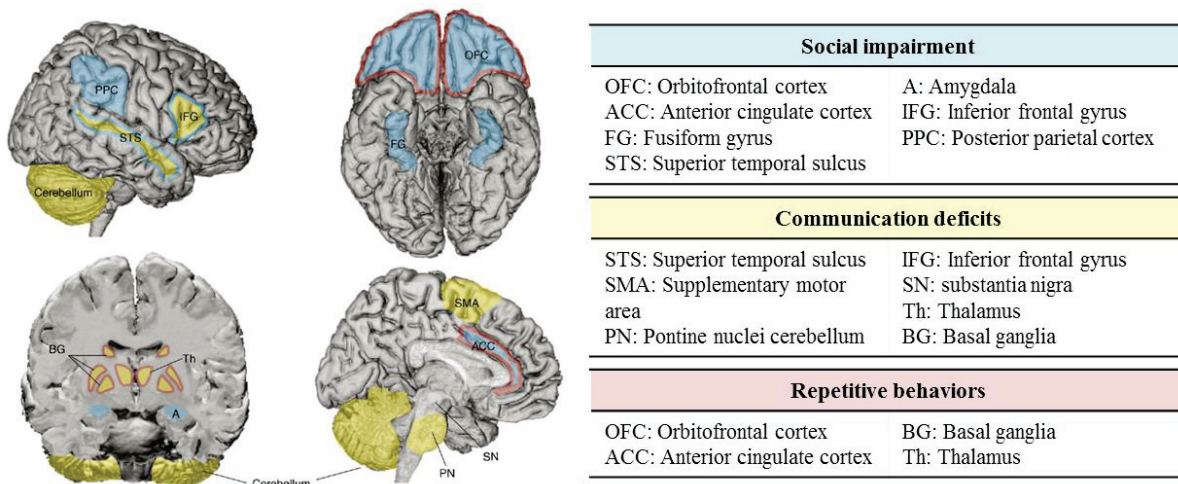
Some brain regions have been particularly studied in ASD and revealed structural abnormalities: the amygdala (involved in social and emotional processing), the cerebellum (involved in sensorimotor functioning), the basal ganglia (involved in motor control and

cognition) and the corpus callosum (Mahajan and Mostofsky 2015). In individuals with ASD, there would be an increased cortical thickness in regions involved in the cognitive functions that are affected in ASD (Hyde et al. 2010). Figure 5 illustrates some of the brain regions involved in the mediation of autistic symptoms, such as social impairment, communication deficits and repetitive behaviors.

In conclusion, cortical development in ASD could be summarized in three phases: accelerated expansion of cortical development in early childhood (mostly the first year), accelerated thinning in later childhood and adolescence (especially in frontal regions), and decelerated thinning in early adulthood (Zielinski et al. 2014). In addition, atypical cellular organization was reported in ASD: mini-columns showed abnormal structure, were smaller and more numerous than in controls (Casanova et al. 2002).

**Figure 5 : Brain areas involved in the mediation of autistic symptoms**

(Figure adapted from Amaral et al. 2008)



### I. 3. B. Brain functional and connectivity patterns in ASD

Many fMRI studies have linked regional hyper- or hypo-activations with symptoms or impaired abilities in ASD, such as language development, emotion perception, repetitive behaviors, social interaction perception, and sensory processing (Ha et al. 2015). For instance, amygdala enlargement was associated with impaired social and communication functioning (Kim et al. 2010), while local grey matter decrease in regions belonging to the mirror system<sup>2</sup> was associated with symptom severity in ASD (Hadjikhani et al. 2006).

<sup>2</sup> Mirror neurons are activated both by action execution and action observation. In humans, it encompasses the inferior frontal gyri, precentral gyri, supplementary motor area, and inferior parietal lobule.

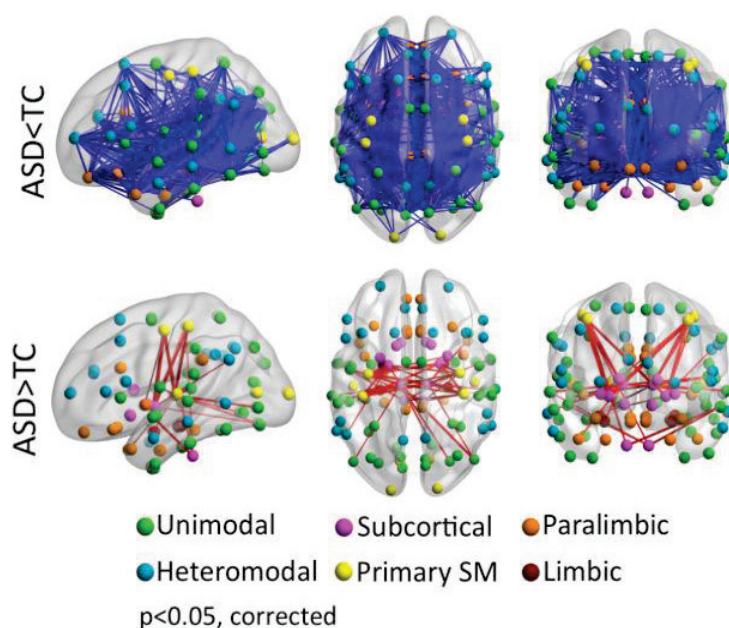


Several studies demonstrated atypical patterns of structural connectivity in ASD. DTI studies showed short-range hyper-connectivity in ASD (Courchesne and Pierce 2005; Shukla et al. 2011). The local hyper-connectivity could emerge from migration defects, excessive neurogenesis, reduced apoptosis or neuroinflammatory reactions (Courchesne and Pierce 2005). Besides, structural long-range cortical hypo-connectivity (frontal-posterior) has been frequently observed in ASD (Courchesne and Pierce 2005; Anagnostou and Taylor 2011; Just et al. 2012). Both the abnormal brain enlargement in the second year of life, and the reduced long-distance connections would lead to an altered brain organization (Lewis et al. 2013).

Functional MRI studies in ASD showed both hyper- and hypo- functional connectivity patterns, depending on the task. Notably, in task-based functional connectivity studies, hypo-connectivity in ASD was reported in tasks associated with language, working memory, mental imagery, face processing, facial expression recognition, executive functions, visuospatial coordination, cognitive control and social cognition (Uddin et al. 2013; Ha et al. 2015).

The Autism Brain Imaging Data Exchange investigated the whole-brain intrinsic functional connectivity based on more than 1000 resting-state functional MRI studies of control and ASD subjects. They found that even though both hyper- and hypo-connectivity were present in ASD, functional hypo-connectivity was strikingly dominant (Di Martino et al. 2014) (Figure 6). Hyper-connectivity was specifically marked for cortico-cortical and interhemispheric functional connectivity in ASD (Di Martino et al. 2014).

**Figure 6 : Whole-brain functional connectivity in ASD**  
(Di Martino et al. 2014)



Significant group differences (ASD vs. Typical Controls [TC]) for intrinsic functional connectivity between each of the 112 parcellation units included in the structural Harvard-Oxford Atlas. Parcellations are represented with their center of mass as spheres.

Upper panel: intrinsic functional connections (blue) weaker in ASD vs. TC.

Lower panel: intrinsic functional connections (red) stronger in ASD relative to TC.

Displayed results are corrected for multiple comparisons using false discovery rate at  $p < .05$ .

To summarize, structural connectivity shows long-range under-connectivity and short-range over-connectivity, and functional connectivity mostly shows hypo-connectivity in ASD. However, Picci and colleagues underlined that these findings need to be taken cautiously because there is also contradictory evidence, and because distance and strength of connectivity are not sufficient to explain atypical neural connectivity in ASD (Picci et al. 2016). Importantly, variables such as transient head motion (e.g. in children with ASD) can artificially suggest group differences in structural and functional connectivity (Yendiki et al. 2014; Picci et al. 2016). It is also important to take into account the developmental perspective, since intrinsic functional connectivity appears to mostly increase in children with ASD, whereas it appears to decrease in adolescents and adults with ASD (Uddin et al. 2013).

### *I. 3. C. Neurobiology and molecular specificities of ASD*

The neurobiology of ASD can be assessed by post-mortem studies, tissue sampling, positron emission tomography (PET) or magnetic resonance spectroscopy (MRS). MRS is a non-invasive method measuring *in vivo* metabolite concentrations in a region of interest. Proton MRS measures concentrations in choline containing compounds (Cho), Cr (creatine and phosphocreatine), Glx (glutamate, glutamine, and GABA), myo-inositol, and N-acetylaspartate. GABA MRS specifically measures GABA levels. Some variations in metabolite concentrations have been linked to autistic symptoms. For instance, in ASD, decreased glutamate and Cho concentrations were associated with impaired social communication deficits (Horder et al. 2013; Doyle-Thomas et al. 2014; Tebartz van Elst et al. 2014), and decreased Cho concentration was associated with more restricted and repetitive behaviors (Doyle-Thomas et al. 2014).

#### ***Glutamate and GABA***

GABA MRS studies revealed a reduced GABA concentration in ASD in frontal (Harada et al. 2011), sensorimotor (Puts et al. 2016) and auditory regions (Gaetz et al. 2014). In the visual cortex, GABA concentration was not reduced in ASD (Gaetz et al. 2014), but GABAergic action was reduced in the context of a binocular rivalry task (Robertson et al. 2016). Decreased GABA concentration in the anterior cingulate cortex has been associated with higher autistic severity (Brix et al. 2015). Importantly, most of the studies revealing differences between ASD subjects and controls were performed in children, and results on adults remain scarce and often inconclusive (Ford and Crewther 2016).

Defaults of maturation of GABAergic neurons were suggested in ASD (Marrosu et al. 1987; Yamada et al. 2004; Ben-Ari et al. 2012). In immature GABAergic neurons, intracellular chloride ( $\text{Cl}^-$ ) level is relatively elevated. As a consequence, GABA binding on post-synaptic receptors results in the exit of  $\text{Cl}^-$ , leading to depolarization and so activation. In mature GABAergic neurons, as the intracellular chloride level is reduced (following chloride exporter expression),  $\text{Cl}^-$  enters into the neuron after GABA binding, leading to hyperpolarization and subsequently inhibition. A strategy to help these neurons to mature would be to use the diuretic bumetanide, since it inhibits the chloride importer and thus reduces neuronal chloride levels, to mimic mature GABA neurons.

Bumetanide administration would lead to a reduction of the autistic symptoms in some children with ASD (Lemonnier and Ben-Ari 2010; Lemonnier et al. 2017) and to an improvement of emotional face perception in adolescents and young adults with ASD (Hadjikhani et al. 2015). In addition, ASD children who were treated with bumetanide combined with ABA training showed better outcomes than those with ABA training only (Du et al. 2015). Besides, the administration of GABA agonists and glutamate receptor antagonists shows promising preliminary results in ASD (Oberman 2012).

Hence, both GABA action and concentration would be decreased in ASD. The reduction in GABA could be due to a decrease in GAD (Glutamic acid decarboxylase), which is the enzyme converting glutamate into GABA. Indeed, in ASD, the concentration of this enzyme was reduced by 48% to 61% in parietal and cerebellar cortices in a post-mortem study (Fatemi et al. 2002). ASD would be characterized by higher glutamate levels, lower GABA levels, and so, by an increased glutamate/GABA ratio (Lam et al. 2006; Rosenberg et al. 2015). An increased glutamate/GABA ratio would be associated with aberrant neuronal development and abnormal connectivity (Bittigau and Ikonomidou 1997), especially in the second year of life when glutamate concentration peaks.

### ***Other neurotransmitters***

Abnormal concentrations of other neurotransmitters, such as serotonin, dopamine, norepinephrine, acetylcholine, oxytocin and opioids were also reported in ASD (see Lam et al. 2006, for a review). Serotonin, known to regulate brain development, is increased by 50% in about one third of individuals with ASD (Schain and Freedman 1961; McBride et al. 1998).

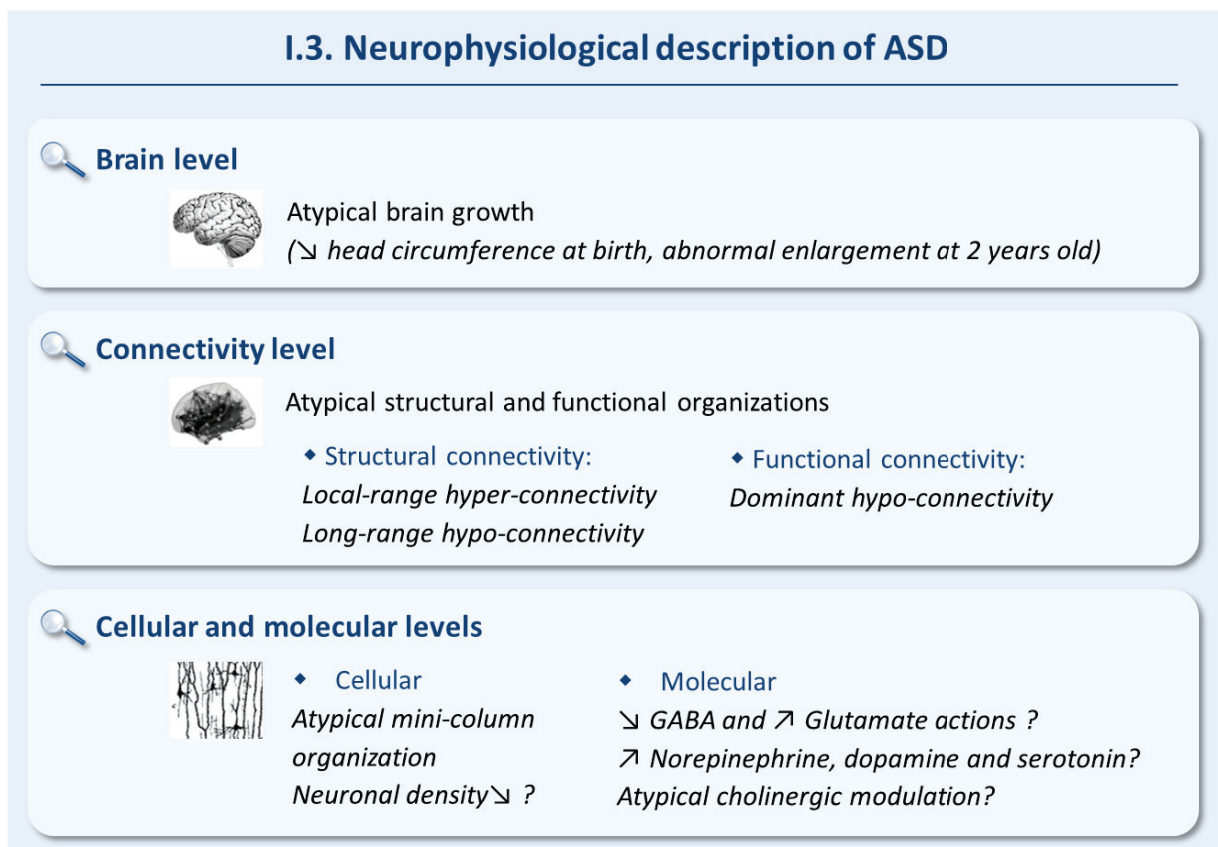
Pharmacological studies using dopaminergic blockers show decreased stereotypies in ASD, suggesting an hyperactive dopaminergic system in ASD (Lam et al. 2006). Norepinephrine (synthesized from dopamine) is notably involved in filtering irrelevant

information, attention, anxiety and memory (Amaral and Sinnamon 1977). Blood concentration of norepinephrine would be increased in ASD (Lake et al. 1977; Lam et al. 2006), but importantly, blood concentration might not reflect concentration in the brain.

Cholinergic neuromodulation also showed abnormalities, with reduced number and affinity of cholinergic receptors the parietal, frontal and cerebellar cortex of individuals with ASD (Perry et al. 2001; Lee et al. 2002). Increased cholinergic neuromodulation in the caudate nucleus of a mouse model ASD led to decreased cognitive rigidity and less social deficiency (Karvat and Kimchi 2013). These two findings suggest decreased cholinergic modulation in ASD. However, brain-derived neurotrophic factor concentration was higher in ASD, and this factor promotes survival of cholinergic neurons (Perry et al. 2001).

In conclusion, genetic, epigenetic, and environmental factors would lead to synaptic dysfunctions in ASD, bringing on brain structural and functional abnormalities. In ASD, peculiarities can be observed at the molecular, cellular and brain levels (summarized in Figure 7). All of these aspects might contribute to the core symptoms of ASD. Confronting results from behavioral, genetic and neuroimaging studies might help defining neuroendophenotypes of ASD.

**Figure 7 : Summary of part I.3**



## ***I. 4. Theoretical models of ASD***

### ***I. 4. A. Theories focused on the core symptoms***

#### **◆ *Theory of mind***

Some of the first theories of ASD questioned whether individuals with ASD would have an impaired theory of mind. The theory of mind (ToM) refers to the ability to impute and recognize mental states of oneself and of other people, with mental states including purpose, intention, belief, thinking or doubt (Premack and Woodruff 1978).

In 1985, it was suggested that the impaired social abilities of individuals with ASD could be explained by an impaired ToM (Baron-Cohen et al. 1985). To test the hypothesis of a deficit of ToM, they used the Sally and Anne test in children with ASD. In this test, children observe a scene where a girl named Sally places a marble into her basket and leaves the room. Anne transfers the marble into her box, and Sally comes back. The children are asked the following belief question: “*Where will Sally look for her marble?*”. If a child points to the previous location of the marble (the basket), it means that he/she appreciates that his/her own knowledge is different from Sally’s, who has a false belief. As Baron-Cohen et al. (1985) found that 80% of the tested children with ASD failed at the belief question, they concluded on a specific deficit of ToM in ASD.

Surprisingly, despite less than 20% of the autistic children passing the Sally and Anne false belief test, 74% of the children with ASD passed the Dot-Midge task which is very close to the Sally and Anne test (Peterson et al. 2013). The main difference between these two tasks is that in the Dot-Midge task, the child competes against a real-life adversary for a desired price hidden in a box. The authors advanced that children with ASD can track others’ beliefs in a competitive game where they are motivated enough (Peterson et al. 2013). In general, adults with ASD succeed at standard ToM tests, but show compromised ToM for moral judgments (Moran et al. 2011).

#### **◆ *Executive functions***

Impaired executive functions in ASD was another model that was initially proposed to explain autistic symptoms (Damasio and Maurer 1978; Ozonoff et al. 1991; Russell 1997). Executive functions is an umbrella term for the flexible control of goal directed behaviors,

which encompasses working memory, cognitive flexibility, monitoring, planning and inhibition, and which involves the prefrontal cortex (Roberts et al. 1998; Funahashi 2001).

The idea of impaired executive functions in ASD emerged from observations showing that individuals with ASD have a low performance at executive functions tasks assessing mental flexibility (Rumsey and Hamburger 1990; Ozonoff et al. 1991), or planning capacities (Ozonoff et al. 1991). In ASD, impaired cognitive flexibility and planning was associated with social difficulties (Pennington and Ozonoff 1996; Hill 2004; Kenworthy et al. 2008).

#### ◆ ***Social motivation***

More recently, the *social motivation theory of ASD* was formulated (Chevallier et al. 2012). Social motivation refers to “*a set of psychological dispositions and biological mechanisms biasing the individual to preferentially orient to the social world (social orienting), to seek and take pleasure in social interactions (social reward), and to work to foster and maintain social bonds (social maintaining)*” (Chevallier et al. 2012). This theory suggests that ASD could be characterized by an overall decrease in the attentional weight assigned to social information. This impairment in social attention would occur early in development, therefore depriving children with ASD of adequate social learning experiences. This early decrease in social attention is consistent with eye-tracking studies in young children with ASD demonstrating decreased orienting to social stimuli (Pierce et al. 2011; see Chevallier et al. 2012 for a review). The authors suggest that these deficits are linked with disruptions of the orbitofrontal-striatal-amygdala circuitry, therefore decreasing the reward value of social stimuli.

### ***I. 4. B. Theories focused on perception***

Non-social abnormalities noticed by Kanner and Asperger included restrictive repertoires of interest, obsessive desire for sameness, islets of ability, excellent rote memory and preoccupation with parts of objects (Kanner 1943; Asperger 1944).

#### ◆ ***Weak central coherence theory***

Frith suggested that individuals with ASD would process perceptual information differently than controls (Frith 1989). Indeed, controls would tend to process stimuli globally, often omitting details, so as to extract its overall meaning. Bartlett (1932) had called this tendency a “*drive for meaning*”, while Frith (1989) named it the “*central coherence*”. Frith

suggested that subjects with ASD could be characterized by a *weak central coherence* (WCC), and so by a decreased global processing (Frith 1989). In 2006, Happé and Frith refined their theory, and suggested that instead of a core deficit in central processing, it could be a processing bias towards a superiority in local-focused processing (Happé and Frith 2006). As deficits in social cognition could hardly be explained by the WCC model, they suggested that WCC may occur alongside impaired social cognition. The process in which the global picture is missed would also affect language understanding abilities (Järvinen-Pasley et al. 2008).

According to the WCC theory, individuals with ASD would be advantaged in tasks where attention to local information is required, but disadvantaged in tasks where the global meaning needs to be extracted. It suggests that people with ASD tend to have a fragmented perception rather than a global picture. The WCC theory is supported by studies showing that individuals with ASD fail to extract regularities to categorize or generalize (Klinger and Dawson 2001; Dawson et al. 2005; Church et al. 2010; Vladusich et al. 2010; Gastgeb et al. 2012) and show increased local processing (e.g. Dakin and Frith 2005). The WCC theory was also tested with embedded figure tasks, which consist of finding a target figure within a more complex figure. Subjects with ASD were faster than controls, or as fast as them, at the embedded figure tasks, therefore suggesting increased local processing (see Horlin et al. 2016, for a review).

#### ◆ ***Enhanced Perceptual Functioning***

The *Enhanced Perceptual Functioning (EPF)* is an alternative to the WCC theory (Mottron and Burack 2001; Mottron et al. 2006). This model intends to account for the superior discrimination and performance found in individuals with ASD, mostly in the visual and auditory modalities (Dakin and Frith 2005; Samson et al. 2005). It emerged from observations of autistic savant skills, peaks of ability, and superior perception. In comparison to the WCC, the EPF theory focuses on an increased perceptual ability in ASD rather than a deficit or bias. They postulated that ASD was not characterized by an inability to integrate parts into a whole, but by an absence of precedence for global stimulus characteristic. The revisited model of the EPF is based on eight principles (Mottron et al. 2006). Among these principles are: a locally oriented default setting in ASD, early atypical autistic behaviors explained as a regulation of perceptual inputs, atypical activation in perceptual brain regions and perceptual expertise underlying savant syndrome. Caron et al. (2006) reported superior

low-level processing in visuospatial tasks in ASD, and concluded that these ability peaks were more in favor of the EFP theory than the WCC model.

A few years later, Mottron et al. (2013) proposed an extension of the EFP theory: *the mechanism of veridical mapping (VM)*. The VM theory intends to explain the high prevalence of savant skills in autism, in particular with hyperlexia, absolute pitch and synesthesia (Burd et al. 1985; Jones et al. 2009; DePape et al. 2012; Neufeld et al. 2013). Savant skills are more frequent in individuals with ASD than in any other neurological group (Howlin et al. 2009). According to the VM model, peaks in abilities in subjects with ASD would be due to enhanced coding properties of local neural network, increased connectivity within and between modalities, and enhanced functioning of perceptual areas (Mottron et al. 2013).

#### ◆ *Hyper-systemizing theory*

Autistic savant abilities were also taken into account in the *Hyper-systemizing theory* (Baron-Cohen et al. 2009). In agreement with the WCC, this theory postulates an excellent attention to detail on ASD, however, it suggests that this would be due to sensory hypersensitivity. Attention to details would be directed toward the detection of rules, with input-operation-output reasoning. According to this theory, talent in ASD would emerge from their ability to recognize repeating patterns in stimuli and to generate rules that would help predicting how a system behaves. Hyper-systemizing in ASD would explain savant skills such as spotting prime numbers, calendrical calculation or realistic drawing (Baron-Cohen et al. 2009a). However, the application of this theory to low-functioning autistic individuals remains more challenging, even though the authors suggest that hyper-systemizing could also explain narrow interests, repetitive behaviors and need for sameness, in the sense that a stable context contributes to not perturbing the systemized rules. Baron-Cohen supplemented his theory with the *Empathizing-systemizing theory*, arguing that two factors are necessary to explain both social and non-social symptoms in ASD (Baron-Cohen 2009). The empathizing part of this model refers to impaired ToM in ASD, while the systemizing part refers to the hyper-systemizing theory.

#### ◆ *Reduced Generalization*

Plaisted (2001) introduced the *Reduced generalization model* as an alternative to the WCC model, since the WCC did not take into account all of the perceptual and social peculiarities of ASD. She considered that attentional and perceptual abnormalities in ASD are due to reduced generalization, seen as a decreased processing of the similarities or regularities



encountered between stimuli or situations. Two stimuli need to share sufficient features in common in order to be categorized together; otherwise they will be regarded as different. The *reduced generalization model* suggests that people with ASD would poorly process similarities between stimuli, and would tend to view stimuli as different even though they share common features. This would explain poor transfer, as well as impaired generalization and categorization observed in ASD (Ozonoff and Miller 1995; Church et al. 2010). In contrast, subjects with ASD would be better at detecting unique features in stimuli, which is in accordance with their enhanced discrimination abilities (Plaisted et al. 1998). Reduced generalization could be due to reduced associative excitation between encoded elements, caused by an excessive lateral inhibition between neurons (Gustafsson 1997; Plaisted 2001).

#### ◆ *Atypical learning-style strategies*

The assessments made on generalization in the *WCC* and *Reduced Generalization* models could also be done based on a different learning style in ASD. Qian and Lipkin (2011) supported this view, and proposed a *Learning-style theory of ASD*. They defined two main learning styles: the lookup table (LUT) learning style where individuals store each experience precisely (e.g., associations between phone numbers and names), and the interpolation (INT) learning style where individuals extract regularities from stimuli to generate rules. In a noisy environment, the LUT style would be poor at extracting information since it would focus on non-informative details and would not compress information. As compared to controls, individuals with ASD would present a bias toward the LUT learning style. This bias could explain why the detection of regularities would be impaired both in social and non-social contexts in ASD.

### *I. 4. C. Theories focused on neural properties*

#### ◆ *Brain plasticity*

The previous theories mostly emerged from observed autistic symptoms, whereas other theories were formulated based on neural mechanisms. One core mechanism mentioned by these theories is brain plasticity, referring to structural or functional changes in the nervous system, which takes place over lifetime. Brain plasticity involves neuronal deletion as well as synaptic pruning and reorganization, occurring during development, learning, memory, habituation or brain repair processes. Some abnormal anatomical or functional properties of individuals with ASD could be related to atypical brain plasticity. Indeed, the abnormal cell

division and apoptosis (Polšek et al. 2011), reduced long-distance connectivity and increased short-distance connectivity (Dichter 2012; Kana et al. 2014) and atypical brain size evolution and morphological abnormalities (Courchesne 2003; Amaral et al. 2008) provide arguments for theories of impeded plasticity in ASD.

### *Intense World Syndrome*

The *Intense World Syndrome theory* was inspired from molecular, cellular and behavioral results in valproic acid (VPA) rat models of autism (Markram et al. 2007; Markram and Markram 2010). According to this theory, hyper-reactivity and hyper-plasticity of local neuronal circuits could explain the autistic neuropathology. This theory focuses on hyper-functioning of local circuits in the neocortex and in the amygdala. The hyper-functioning model relies on studies showing increased neuronal responses in VPA rat models (Rinaldi et al. 2008). Hyper-functioning could be due to hyper-connectivity in neocortical microcircuits: connectivity between pyramidal neurons is increased by 50% in VPA rat models (Rinaldi et al. 2008). Excessive neuronal processing in the neocortex could account for the hyper-attention, hyper-perception and hyper-memory encountered in ASD, leading to an intense and painful experience of the world. Hyper-reactivity in key regions for social cognition, such as the amygdala, could lead to overwhelming emotions and withdrawal from social situations. This idea comes from rat studies, but is in contradiction with findings showing hypo-activation of the amygdala in subjects with ASD (Baron-Cohen et al. 1999, 2000; Pierce et al. 2001). Finally, the authors interpret repetitive behaviors and routines as being a consequence of excessive neuronal learning, which would trap individuals into these restrictive repertoires of behaviors. Arguments for an increased learning are found in animal studies showing hyper-plastic glutamatergic synapses and boosted postsynaptic plasticity in VPA rat models (Rinaldi et al. 2007). However, it is important to underline that this theory is mostly based on rat models of ASD.

### *The Trigger-Threshold-Target model*

The *Trigger-Threshold-Target (TTT) model* assumes that alterations in experience-dependent plasticity are central in ASD (Mottron et al. 2014). This suggestion is based on three observations: (1) the most plastic cortical regions control the main cognitive domains affected in ASD, (2) sensory deprivation share several features with ASD in terms of cortical and functional reorganization, (3) genetic mutations and/or environmental factors mostly affect developmental brain plasticity. According to the TTT model, a certain number of

elements are required for ASD to occur: “*a genetic mutation triggers a neuroplasticity reaction in individuals with a genetically-determined low threshold*” in a specific neurofunctional *target* region (Mottron et al. 2014). The target region with enhanced plasticity would be language regions in the case of Asperger syndrome, and perceptual cortices in the case of autism. Other brain regions would then be neglected, such as those involved in social and motor behaviors in individuals with Asperger syndrome. The variability in autistic phenotypes would depend on the combination between the genetic triggers and thresholds, and brain targets. Autistic peaks in abilities could rise from cortical reallocation processes (Samson et al. 2012) or atypically enhanced connectivity (Kikuchi et al. 2013).

#### ◆ **Neural noise**

##### *High neural noise*

Rubenstein and Merzenich (2003) suggested an *increased ratio of excitation/inhibition* in ASD. The balance between excitation and inhibition depends on the relative number and activity of glutamatergic and GABAergic neurons (which roughly correspond to 80% and 20% of the brain neurons, respectively). Reduced GABAergic action results in an increased excitatory state of the brain and increased noise in the cortex. Increased ratio of neural excitation to inhibition in ASD was supported by recent computational simulations (Rosenberg et al. 2015). As previously detailed, ASD would be characterized with reduced GABA concentration and action (Ford and Crewther 2016; Puts et al. 2016; Robertson et al. 2016). High cortical noise during development could induce an over-representation of stimuli by non-differentiated systems, and could lead to aversive reactions to sensory stimuli (Rubenstein and Merzenich 2003). According to their model of ASD, multiple gene alterations with differential penetrance, combined with potential exposition to environmental factors, could increase the excitation/inhibition ratio.

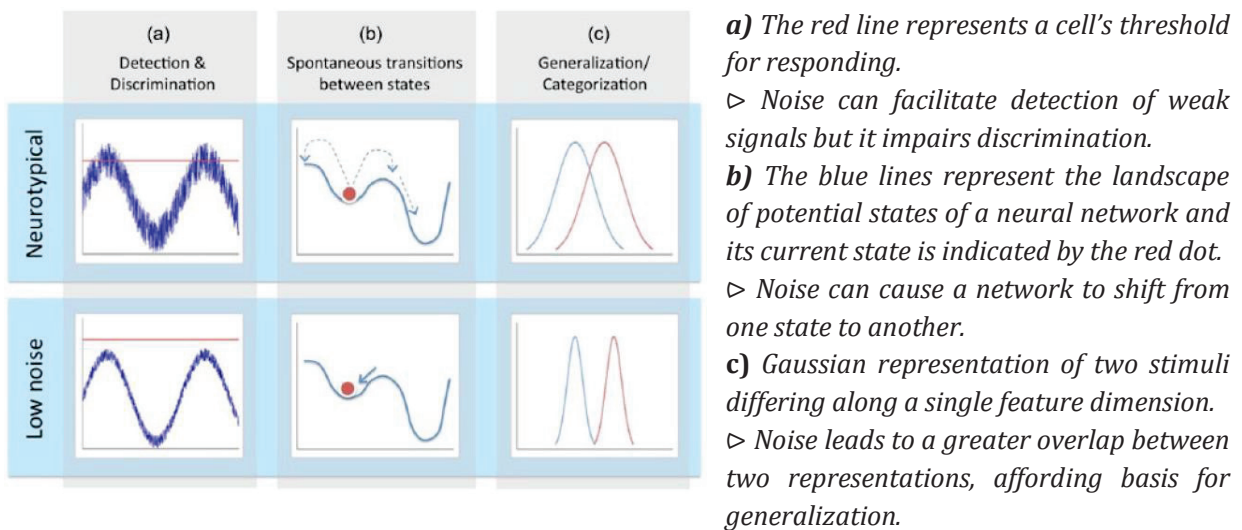
This view of an *increased neural noise in ASD* was also supported by Simmons and colleagues (Simmons et al. 2007, 2009). Based on studies investigating visual processing in ASD, they argued that results were in favor of an increased internal noise in ASD (Simmons et al. 2009). The increased intra-subject trial-to-trial variability found in participants with ASD could be seen as an argument for high neural noise in ASD (Milne 2011). Increased neural noise could lead to sensory overload or hyposensitivity (Simmons et al. 2007; Simmons and Milne 2015). This atypical perception could affect the understanding of social

stimuli. The authors suggested that the noise could result from an increased crosstalk within the cortex or from modifications in the glutamatergic and GABAergic synapses.

### *Low neural noise*

In contrast, Davis and Plaisted-Grant (2015) suggested a *low endogenous neural noise* in ASD. Reduced noise would enhance detection and discrimination in ASD. They first developed the three main actions of noise in neural networks (Figure 8), before explaining how a reduced neural noise could explain many autistic features (Davis and Plaisted-Grant 2015).

**Figure 8 : Action of noise on neural networks**  
(Davis and Plaisted-Grant 2015)



A reduced neural noise in ASD would lead to (1) impaired detection of weak signals and enhanced discrimination, (2) a tendency to remain in the nearest stable state, (3) impaired generalization and categorization, but enhanced discrimination between two close stimuli. Davis and Plaisted-Grant (2015) argued that the research literature of detection and discrimination thresholds is in favor of a low noise account in ASD. Discrimination of targets from non-targets should be enhanced by low neural noise, providing better results in visual search tasks (Plaisted et al. 1998; O'Riordan and Plaisted 2001; O'Riordan et al. 2001; Kaldy et al. 2011). The second prediction of a reduced neural noise in ASD is a tendency to remain in the nearest stable state, which could account for difficulties to make decisions, to shift attention and to switch between tasks. Particularly, repetitive behaviors and restrictive interests encountered in ASD could be due to decreased switching between tasks. Several studies showed that individuals with ASD show less spontaneous and less frequent switches between inputs or perceptual interpretations (Sobel et al. 2005; Robertson et al. 2013).

Finally, the third prediction of a low neural noise in ASD is the impaired generalization and categorization, as two stimuli sharing similar features would be seen as distinct. Hence, subtle differences between two objects would be seen as an actual difference instead of environmental noise. The prediction is in line with the poor categorization, prototype learning, and generalization, already detailed previously.

The low-noise theory resonates with other theories such as the *WCC* (Frith 1989), the *EFP* (Mottron et al. 2006), the *Reduced Generalization* (Plaisted 2001), and the *Learning-style* (Qian and Lipkin 2011) theories of ASD.

#### *I. 4. D. Limitations of these theories*

These theories aim at defining a unifying theory of ASD. However, a frequent drawback is the difficulty to explain every aspect of the autistic symptomology: perception, sensitivity, motor abilities, social abilities, cognitive flexibility, etc. Some of the main limitations are presented below.

First, the hypothesis of an impaired ToM in ASD mostly explains the difficulties in social interactions and communication encountered in ASD, but fails to account for perceptual abnormalities. In addition, a deficit in the ToM cannot explain the autistic symptoms of the 20% of autistic children who pass the Sally and Anne test, the 74% passing the Dot-Midge task, nor the adults with ASD succeeding at these tests.

The WCC theory of ASD and related theories suggest increased local processing and reduced global processing in ASD, but studies often show inconclusive results. For instance, a recent study investigating visuospatial processing in a copying task did not show any differences in local bias or global deficit between ASD and typically developing children (Smith et al. 2016). Furthermore, Van der Hallen et al. (2015) performed a meta-analysis based on 56 studies investigating local and global visual processing in about 1000 subjects with ASD. Group performance neither showed a tendency for enhanced local visual processing nor for impaired global visual processing in ASD. This meta-analysis revealed that subjects with ASD were slower than controls at processing global information (Van der Hallen et al. 2015). Furthermore, differences showing increased local processing and/or decreased global processing abilities in ASD could be related to task instructions, and so, these differences would be due to a disinclination rather than an impaired ability (Koldewyn et al. 2013; Van der Hallen et al. 2016). In addition, enhanced perceptual abilities in ASD

could be context and stimulus dependent. For instance, a study revealed that subjects with ASD had enhanced perceptual abilities for visual simple stimuli, but impaired abilities for more complex stimuli (Bertone et al. 2005). In their study, complex versus simple stimuli referred to second-order versus first-order information, as second-order information recruited more extensive neural circuitry.

Besides, theories based on atypical brain properties also have limitations. The intense world syndrome is based on rat models of ASD, which limits its application to humans. Theories of an increased or decreased neural noise in ASD have difficulties explaining both hypersensitivity and hyposensitivity, and the high noise theory could hardly explain enhanced discrimination abilities found in ASD.

Finally, theories like the *Empathizing-systemizing theory* suggesting two independent mechanisms to explain ASD symptomology are less parsimonious than the ones suggesting that one underlying mechanism could explain ASD peculiarities in every domain.

#### *I. 4. E. Theories focused on the build-up of internal references*

##### ◆ *Mirror neuron system*

Mirror neurons were first discovered in the premotor area of macaques, and have the particularity to fire not only during action execution, but also during action observation (di Pellegrino et al. 1992; Rizzolatti et al. 1996). In humans, the mirror neuron system (MNS) encompasses the inferior frontal gyrus, the inferior parietal lobule, the lower parts of the precentral gyrus and the supplementary motor area (Gallese et al. 1996; Rizzolatti et al. 1996; Hari et al. 1998; Cochin et al. 1999; Rizzolatti and Craighero 2004; Kilner et al. 2009). By allowing individuals to embody the action performed by another person, the MNS would help understanding the goal of others' actions and would also be involved in empathy, in inferring others' states of mind, in acquiring language and in imitating others (Rizzolatti and Craighero 2004; Gallese et al. 2013).

A *broken mirror hypothesis* of ASD was introduced, based on observations of decreased cerebral responses in ASD individuals observing actions (Williams et al. 2001; Cattaneo et al. 2007; Rizzolatti and Fabbri-Destro 2010). EEG studies were in favor of a decreased MNS activity in subjects with ASD watching actions performed by others (Oberman et al. 2005; Martineau et al. 2008), but not when they were watching actions performed by their own hand or by a familiar one (Oberman et al. 2008). Review on fMRI

studies suggested a dysfunction of the MNS in ASD during action observation and imitations (Yang and Hofmann 2016), especially for fMRI studies using emotional stimuli (Hamilton 2013). In ASD, an impaired functioning of the MNS would lead to decreased ability to infer others' intentions in the motor and social domains.

One of the limitations in inferring the cause of others' actions with the MNS is that identical movements can be made for different goals (Kilner et al. 2007a). In order to solve this problem, the MNS can be reinterpreted within the Bayesian or predictive coding frameworks (Kilner et al. 2007a, 2007b). Within these frameworks, the most likely cause of an observed action can be inferred by minimizing prediction error, which corresponds to the discrepancy between sensory inputs (e.g. observed action) and expectations (e.g. previously learnt motor sequences which constitute our prior knowledge). With the MNS, the brain establishes a correspondence between observed motion and its own motor system, so as to infer intention (Schrodt et al. 2015). Hence, understanding and predicting somebody's actions integrates both current motion and prior knowledge about his/her intention in a certain context (Hudson et al. 2016). It therefore relies on internal references learnt throughout past experiences.

#### ◆ *Sensorimotor representations*

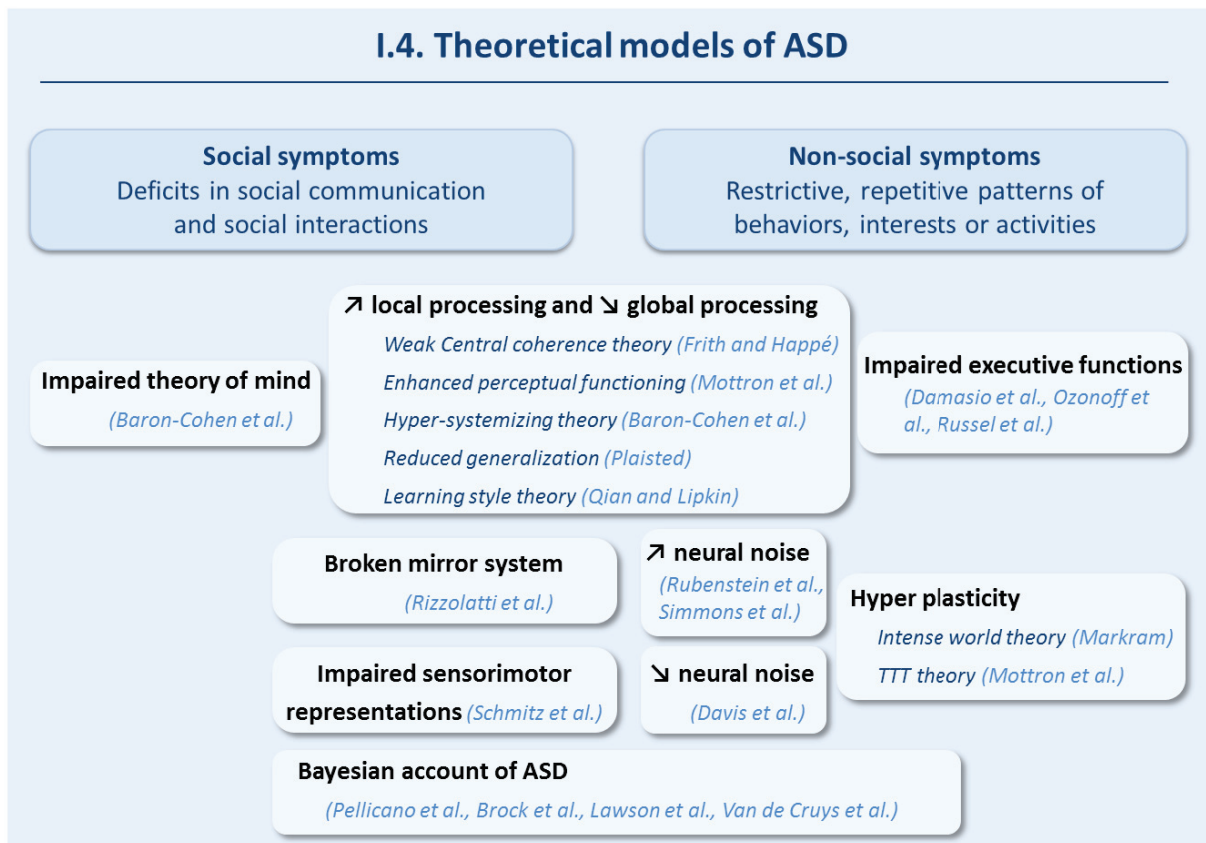
Closely related to the MNS theory of ASD, another theory suggests that ASD could be characterized by difficulties to build up and adjust sensorimotor representations (Schmitz et al. 2003; Schmitz and Assaiante 2008). Action anticipation relies on the sensorimotor representations acquired during previous motor experience (Johansson and Cole 1992; Schmitz et al. 2005). Studies investigating motor control and anticipation in ASD showed decreased anticipatory functions, reduced postural control, decreased prediction of ensuing actions and decreased motor preparation (Rinehart et al. 2001; Molloy et al. 2003; Schmitz et al. 2003; Minshew et al. 2004; Rinehart et al. 2006; Fournier, Kimberg, et al. 2010; Zalla et al. 2010; Brisson et al. 2012). It therefore suggests an impaired learning of sensorimotor internal representations in ASD. Remarkably, a retrospective study based on family movies suggested an anticipation deficit during feeding situations in the infants between four and six months old who were later diagnosed with ASD (Brisson et al. 2012). Within the Bayesian framework, sensorimotor learning would indeed integrate prior knowledge and sensory feedback (Körding and Wolpert 2004).

◆ **Bayesian theories**

Recently, a computational probabilistic view of ASD was presented. Theories based on the Bayesian or predictive coding frameworks propose a unifying view of ASD symptomatology (Brock 2012; Pellicano and Burr 2012; van Boxtel and Lu 2013; Lawson et al. 2014; Sinha et al. 2014; Van de Cruys et al. 2014; Palmer et al. 2017). Bayesian brain theories postulate that the brain is proactive and constantly builds up or adjusts priors. These priors, or expectations, capture the underlying statistical regularities of our environment. Priors help inferring the causes and meaning of stimuli, but also influence our perception. Indeed, percepts emerge from the relative contribution of sensory information and priors. Bayesian theories of ASD suggest that ASD could be characterized by an imbalance in the contribution of priors relatively to sensory inputs. The Bayesian framework and the Bayesian theories of ASD are fully developed in Chapter II. More globally, computational psychiatry offers a new approach to understand psychiatric and neurologic disorders (Stephan and Mathys 2014).

Figure 9 summarizes the main theories of ASD.

**Figure 9 : Summary of part I.4**





## II. Computational approaches of Autism Spectrum Disorders

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### ***II. 1. The Bayesian brain***

#### *II. 1. A. First steps toward the Bayesian brain theory*

##### ***Perception as hypothesis testing***

Over the past century, it has been proposed that our brain tries to infer the causes of our sensations in a similar way as we test scientific hypotheses (von Helmholtz 1866; Gregory 1968, 1980): “*both hypotheses of science and perceptual processes of the nervous system allow recognition of familiar situations or objects from strictly inadequate clues*” (Gregory 1980). Yet, this idea is not so novel, since discussions by Plato, Aristotle and other philosophers, already suggested that individuals would be doing associative processing when perceiving their environments (Tenenbaum et al. 2011).

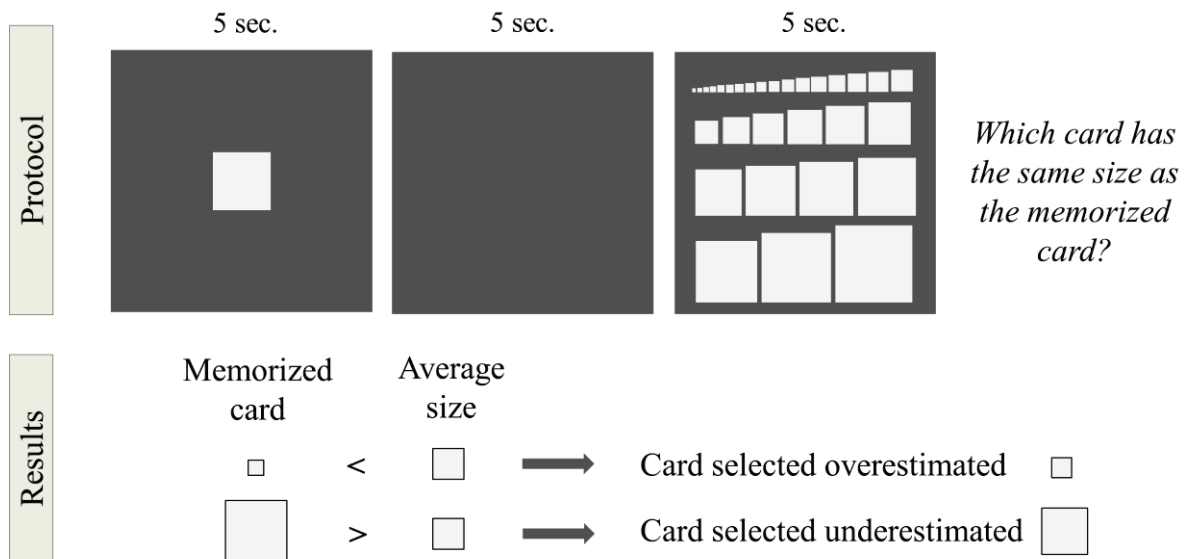
Von Helmholtz had introduced the idea of “*unconscious inference*”, by which implicit knowledge would be incorporated into image formation. This unconscious inference would help disambiguating ambiguous images (von Helmholtz 1866). With the example of the apparent weight of an object, Gregory explained that “*weight is evidently not judged simply by the input from the arm, but also by prior expectation set by the previous handling of weights*” (Gregory 1968). Depending on the context, the brain tries to infer the correct representation, by comparing the incoming sensory input with these *priors*. The hypotheses generated by the brain allow interpolations through data-gaps, but also extrapolations to apply priors learnt in past situations to new ones (Gregory 1980). Perceptual errors or mismatches are generated when the prior differs from the incoming input.

From an evolutionary perspective, we can hypothesize that the ability of the brain to build up prior expectations would have been selected, as it enables a better adaptation to the environment, and so better chances of survival.

**Biased perception toward priors**

In the 1900s, Hollingworth introduced the Central Tendency of Judgment theory, in which he described the influence of internal representations on perception (Hollingworth 1910). He pointed out that when individuals are asked to make a perceptual judgment, they tend to be biased: they judge the feature of a stimulus as being closer to the expected feature value than it actually is. For instance, in his task, participants were presented with square cards of various sizes which had to be memorized (Hollingworth 1910). The presentation of a card was followed by a short delay, and then, participants had to choose the matching card from a set of cards (i.e. the card with the same size as the card previously memorized). The protocol and main results are summarized in Figure 10.

**Figure 10 : Study by Hollingworth (1910)**



Hollingworth noticed that participants tended to select a bigger card when the memorized card was smaller than the average size, whereas they selected a smaller card when the memorized card was larger than the average size. The average size was implicitly learnt throughout the experiment, and constituted the prior knowledge of the participants. This biased perception toward the average magnitude of the feature was called the contraction bias, and was demonstrated in a series of other experiments using visual, auditory and somatosensory modalities (Poulton 1989).

Hollingworth defines the Central Tendency of Judgment as follows: *“Judgments of time, weight, force, brightness, extent of movement, length, area, size of angles, have all shown the same tendency to gravitate toward a mean magnitude, the result being that stimuli above that point in the objective scale were underestimated and stimuli below overestimated,*

*while the mean magnitude itself was invested with no constant error. [...] In all estimates of stimuli belonging to a given range or group, we tend to form our judgments around the median value of the series - toward this mean, each judgment is shifted by virtue of a mental set corresponding to the particular range in question”* (Hollingworth 1910).

Independently from the feature assessed, the judgments would be biased toward the “*indifference point*” (IP) (Hollingworth 1910). The IP is relative, not absolute, since within an experiment, the IP depends on the series limits of the stimuli used, and so highly depends on the context. The IP would influence immediate perception, leading to overestimation or underestimation of the features. The Central Theory of Judgment reflects the incorporation of prior information in psychophysical judgments (Jazayeri and Shadlen 2010).

Interestingly, a task investigating interval timings encoding revealed a central tendency judgment in non-musicians, but not in drummers who must have a more precise encoding of the rhythms than non-musicians (Cicchini et al. 2012). In another temporal reproduction task aiming at eliciting a contraction bias, Karaminis and colleagues suggested that the central tendency reduced with age, as the youngest children tested (between ages 7 and 10 years old) were the ones with the highest bias (Karaminis et al. 2016). Bayesian computational modeling of the results suggested that younger children used stronger priors and had noisier sensory input.

The Central Tendency of Judgment appears to express over the whole spectrum of our sensorium (Kahneman and Klein 2009) and is a strong evidence in favor of a Bayesian account of our perceptual decisions, as it emerges from percepts that are biased by build-up expectations.

## *II. 1. B. Bayesian brain theory*

The Bayesian brain framework considers the brain as a probabilistic machine, constantly making predictions about its environment. In this view, the brain implicitly learns regularities of its environment, to refine its internal representation of the world and to infer the future state of the environment. The brain would actively postulate what is the most likely interpretation of the incoming stimulus in an ambiguous environment, it would be proactive (Bar 2004, 2007, 2009). These predictions would be based on priors or “*scripts*” containing expectations given past experiences, such as scripts storing motor plans (Bar 2009). The implicit learning of statistical regularities of sensory inputs would help inferring its causes,

and would be already performed by newborns and infants (Saffran et al. 1996; Kirkham et al. 2002; Xu and Garcia 2008; Bulf et al. 2011). The Bayesian brain hypothesis could explain how we perceive, predict and interpret our environment (Bar 2007; Clark 2013; Friston 2003, 2012a, 2012b). This probabilistic view of perception is based on Bayes' rule or theorem.

### ***Bayes' theorem***

Thomas Bayes and Pierre-Simon Laplace formulated the Bayes' theorem, which estimates the conditional probability of an event  $A$ , given the event  $B$ . It can be written as follows:

$$P(A|B) = \frac{P(B|A).P(A)}{P(B)} \quad (1)$$

Where  $P(B)$  plays the role of a normalization constant and is given by:

$$P(B) = \int P(B|A).P(A)dA \quad (2)$$

Bayes' rule is thus often reformulated as:

$$P(A|B) \propto P(B|A).P(A) \quad (3)$$

In other words, the posterior probability  $P(A|B)$  is proportional to probabilities  $P(B|A)$  and  $P(A)$ .

### ***Bayesian brain theory***

In the context of the Bayesian brain, the brain assesses the probability of a hypothesis  $H$  to be true given the incoming sensory input  $S$ , based on prior beliefs and the actual sensation. In this context, Bayes' rule can be written as follows:

$$P(H|S) \propto P(S|H).P(H) \quad (4)$$

*Posterior*  $\propto$  *Likelihood* . *Prior*

Hence the percept (*posterior*) results from the combination of sensory evidence (*likelihood*) and current belief (*prior*) on the state of the world. Both the *likelihood* and *prior*

functions are often modeled by Gaussian distributions, of mean  $x$  and precision  $\pi$  (inverse of variance):

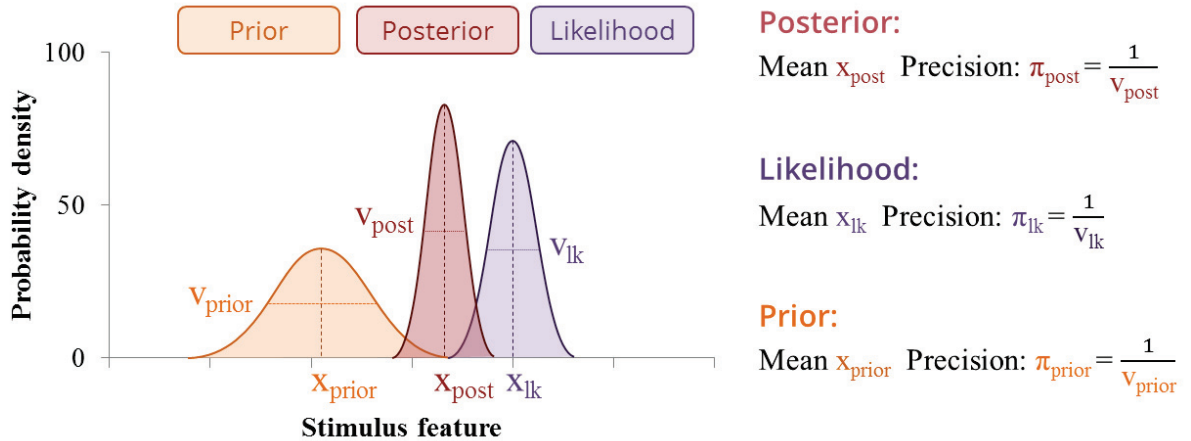
$$\begin{cases} \text{Likelihood} \sim N(x_{lk}, 1/\pi_{lk}) \\ \text{Prior} \sim N(x_{prior}, 1/\pi_{prior}) \end{cases} \quad (5)$$

In this particular case, the combination of the *likelihood* and *prior* distributions results in a Gaussian *posterior* distribution. Computational simulations of cortical neuron networks suggest that neurons represent probability distributions of the stimulus feature, with variable degrees of precision, and combine the distributions according to an approximation of Bayes' rule (Ma et al. 2006). The maximum of the *posterior* probability distribution, centered on  $x_{post}$ , is considered as the best estimate of the feature given the prior and sensory data.

$$\text{Posterior} \sim N(x_{post}, 1/\pi_{post}) \quad (6)$$

Figure 11 illustrates the combination of the *likelihood* and *prior* functions to give a *posterior* function in the simple general case of one-dimensional Gaussian variables.

**Figure 11 : One-dimensional prior and likelihood Gaussian functions and the ensuing Bayesian posterior**



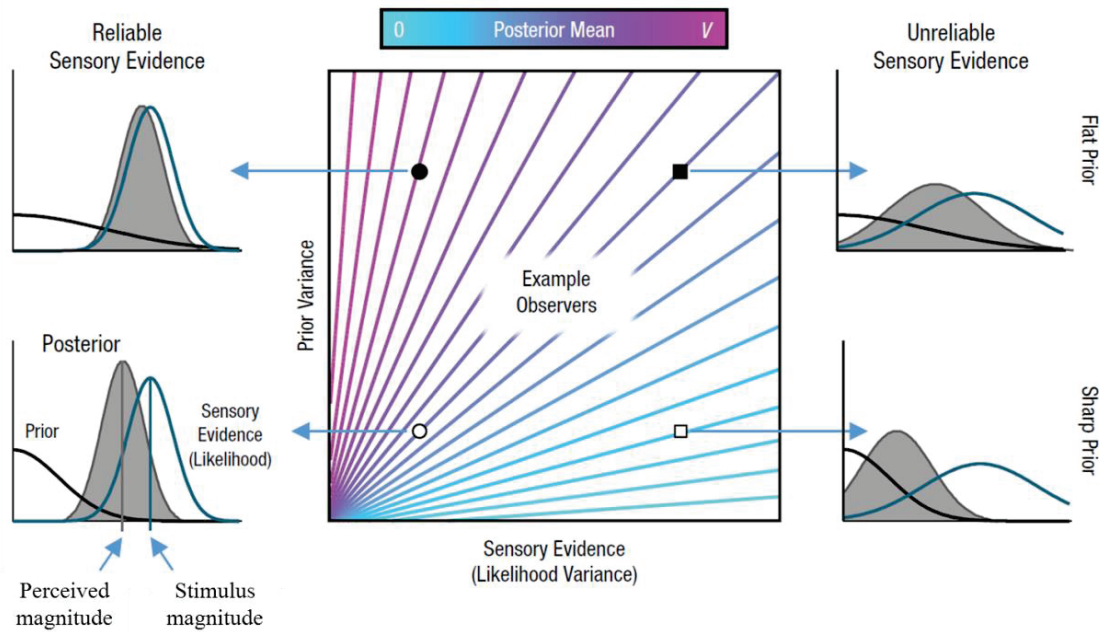
The *posterior* estimate is a linear combination of the *priors* and *likelihood* means, weighted by their respective precisions:

$$x_{post} = \frac{\pi_{prior} \cdot x_{prior} + \pi_{lk} \cdot x_{lk}}{\pi_{post}} \quad (7)$$

$$\pi_{post} = \pi_{prior} + \pi_{lk}$$

The more precise the distribution of the *prior* or *likelihood*, the more influence it has on the *posterior* distribution. In other words, a strong prediction (i.e. precise prior) will greatly bias perception toward the *prior*. Likewise, a noisy sensory signal (i.e. *likelihood* with a wide variance) will induce a *posterior* largely biased toward the *prior* (Tassinari et al. 2006; Tong et al. 2016). The effect of the variance on the distribution of the *posterior* is illustrated in Figure 12.

**Figure 12 : Effect of prior and likelihood variances on posterior distribution**  
(Powell et al. 2016)



*Schematic of the Bayes model of perception (here: example for speed perception).*

*The central panel shows how the variance of the prior distribution and the sensory evidence influence perceived speed (mean of the posterior distribution, color-coded from 0 to stimulus speed V). Each contour corresponds to an observer (identified by symbols in the central panel) with a particular combination of prior variance and level of sensory evidence.*

*Top panels: flat priors. Bottom panels: sharper priors. Sensory evidence (likelihood) becomes less reliable from left to right. In each case, the statistically optimal best guess is based on multiplying the sensory evidence (likelihood function) with the prior distribution to yield the posterior distribution.*

### **Prediction error**

Note that equation 7 above can be rewritten as follows:

$$x_{post} = x_{prior} + \frac{\pi_{lk} \cdot (x_{lk} - x_{prior})}{\pi_{post}} \quad (8)$$

This clearly shows that belief up-dating or the way the prior expectation evolves to form a posterior belief depends on the prediction error term. Prediction error refers to the

difference between the predicted percept (given by  $x_{prior}$ ) and the actual sensation ( $x_{lk}$ ). Importantly, prediction error is weighted by precisions. This weight can be flexibly modulated depending on whether prediction error is informative or not (Clark 2013). Indeed, prediction errors can be used to update the predictive model when they correspond to learnable regularities, and can be ignored when they correspond to intrinsic noise in the environment (Van de Cruys et al. 2013). Precisely, prediction errors signaling intrinsic noise should not be used to update prior mean, but can be used to improve future precision estimate (Van de Cruys et al. 2016).

Following prediction errors (PE), internal representations can be adjusted to improve future predictions (Schultz and Dickinson 2000; Friston 2003). One challenging element to update priors is that the brain needs to “*distinguish whether the uncertainty is caused because our environment has changed, or because we have not yet obtained enough samples in an otherwise stable environment*” (Duzel and Guitart-Masip 2013). For accurate perception, the brain requires to get the best adapted predictive model, minimizing prediction errors (Feldman and Friston 2010; Clark 2013). Indeed, according to the free-energy principle<sup>3</sup>, the objective of perception and action is to minimize surprise (i.e. to avoid prediction errors) (Friston et al. 2006).

As shown above, changes in beliefs are proportional to PE, weighted by the ratio of the precision of the sensory input ( $\pi_{lk}$ ) and of the prior ( $\pi_{prior}$ ) (Mathys et al. 2011).

$$\Delta \text{belief} = \frac{\pi_{lk}}{\pi_{prior}} \cdot \text{prediction error} \quad (9)$$

Predictive coding in the brain suggests that cortical hierarchies implement Bayesian inference such that the relative weight of priors and sensory inputs is controlled by their precisions (Rao and Ballard 1999; Friston 2008). At each level, a comparison is made between top-down predictions and bottom-up incoming signals, giving rise to an upward message passing in the form of a weighted PE and to an up-dated downward prediction (Feldman and Friston 2010; Clark 2013). The higher the hierarchical level, the larger the span of information representations along the temporal and spatial dimensions (Kiebel et al. 2008). Within the predictive coding framework, predictions and prediction errors are considered in several levels of the cortical hierarchy. Low-level versus high-level priors can refer to unique

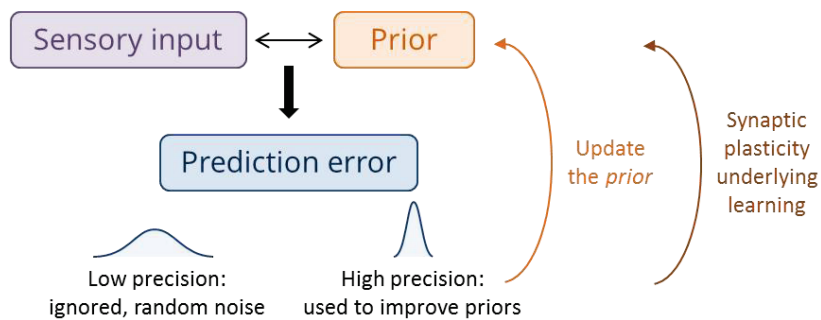
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<sup>3</sup> The free-energy principle says that any self-organizing system that is at equilibrium with its environment must minimize its free energy. Free energy is an information theory measure that bounds or limits the surprise on sampling some data, given a generative model. Here, surprise refers to the negative log-probability of an outcome (an improbable outcome is therefore surprising) (Friston 2010).

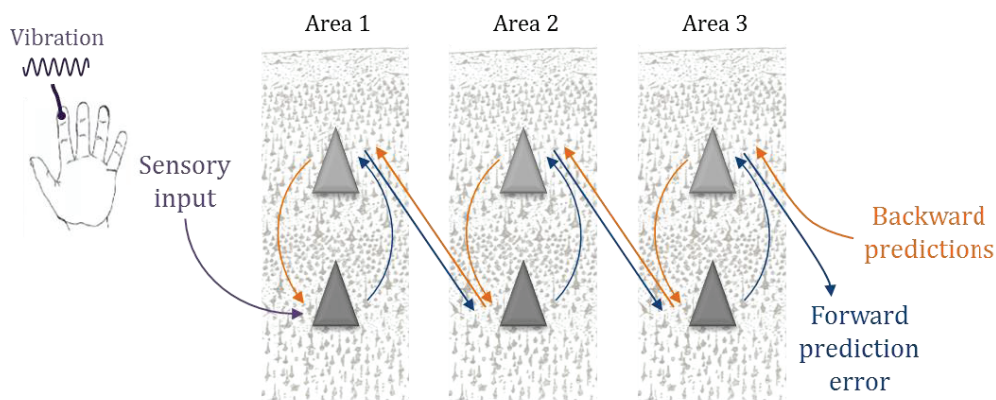
versus multiple features or to simple versus complex stimuli. For instance, extracting only first-order orientation of a stimulus requires early visual regions (i.e. lower level), whereas treating orientation out of noise involves a more extensive neural circuitry (i.e. higher level) (Bertone et al. 2005). Besides, higher-level priors can also refer to hyper-parameters which modulate prior precision (Friston et al. 2013), depending on the volatility of the environment. Hence, higher-level priors can refer to priors including larger time-scales.

Figure 13 illustrates a simplified representation of predictive coding.

**Figure 13 : Prediction error in the predictive coding framework**



*Hierarchical message passing in the brain (inspired from Feldman and Friston 2010)*



### **Bayesian inference in the brain**

In the Bayesian framework, perception is viewed as a compromise between uncertain sensory data and priors based on previous experience, minimizing prediction errors. This minimization can be made by choosing an appropriate action to make the environment match predictions, or by using this signal to adjust beliefs to be better adapted.

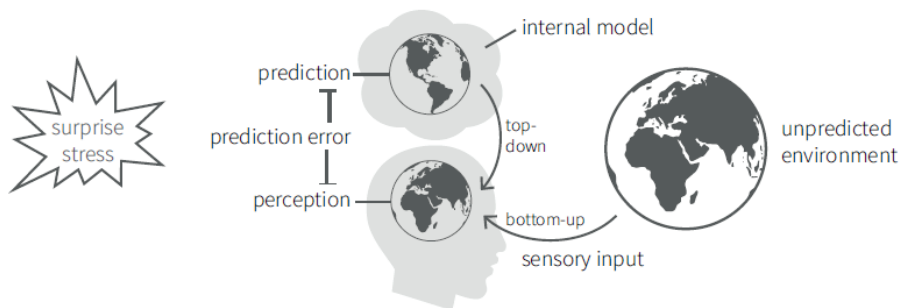
Bayesian inference would be particularly effective in ambiguous environments, since expectations or priors will exert greater influence on perception when sensory data seem poorly reliable as they are noisy (Tong et al. 2016). Priors have two main effects on



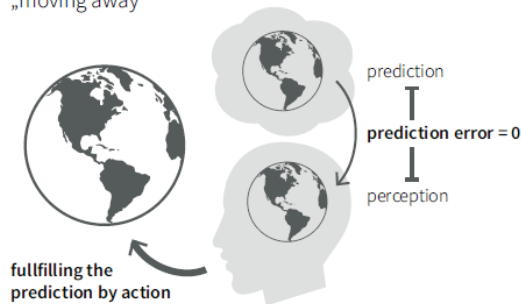
perception. On the one hand, priors facilitate stimuli detection and interpretation, despite the stimulus complexity and the background noise (Seriès and Seitz 2013). On the other hand, global expectations and implicit priors can alter the appearance of a stimulus and bias our perception (Colloca and Benedetti 2005; Petrovic et al. 2005; Sterzer et al. 2008). Bayesian inference in the brain is illustrated by Figure 14.

**Figure 14 : Predictive coding and Bayesian brain**  
(Haker et al. 2016)

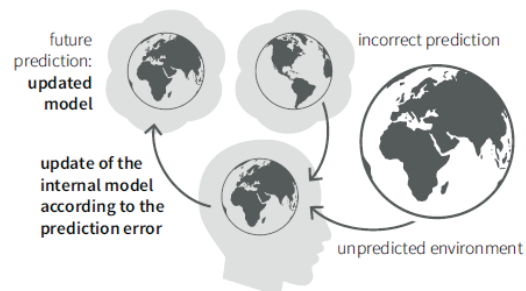
**A Predictive coding in the „Bayesian brain“**



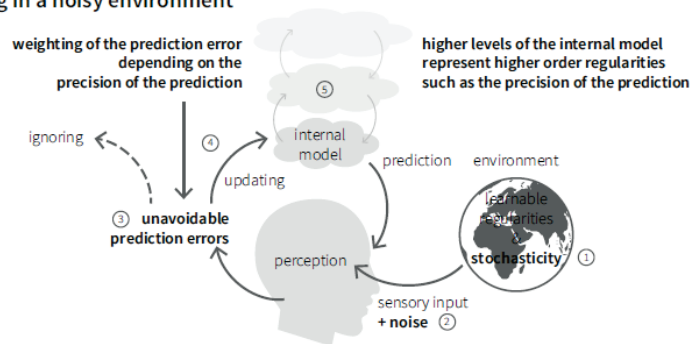
**B Minimising prediction error by action**  
„moving away“



**C Minimising prediction error by learning**  
„explaining away“



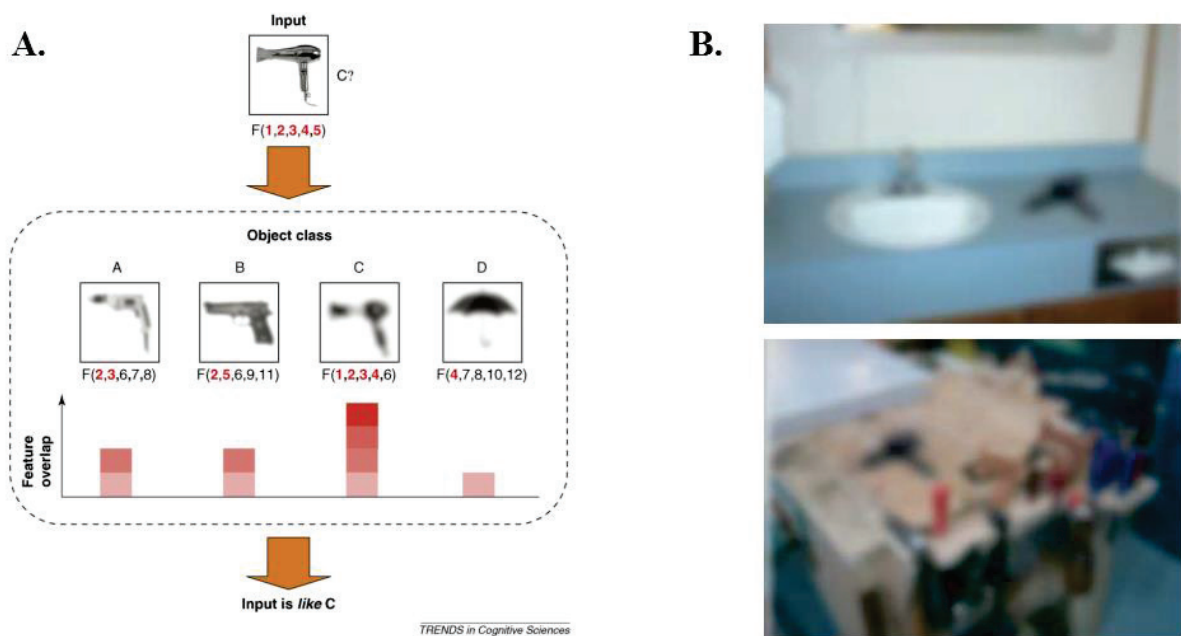
**D Hierarchical Learning in a noisy environment**



- A.** The brain’s homeostatic goal is to minimize prediction errors. Prediction errors can be reduced in two ways: action or learning.
- B.** Predictions can be fulfilled by choosing actions that lead to expected sensory inputs.
- C.** Incorrect predictions can be adapted according to prediction error. Under this model update (learning), the prediction error is explained away.
- D.** Due to stochasticity in the environment (1) and noise of sensory channels (2), prediction errors can usually not be fully explained away (3). Their impact on belief updates depends on the relative precision of sensory input and prediction (4), which is coded in higher levels of the internal model (5).

The role of priors in perception highlights the idea that the brain is a proactive system that constantly generates predictions (Bar 2004, 2007). These memory-based predictions would “*facilitate perception and cognition by pre-sensitizing relevant representations*” (Bar 2007). Predictions would be based upon repeated patterns and statistical regularities found in our environment, stored in memory and enabling associations. Then, the brain would search analogies between a novel sensory input and internal representations (Figure 15). Finally, the brain would translate these analogies and associations into predictions, depending on the overall context. This process would facilitate perception and help interpretation and categorization of the stimulus.

**Figure 15 : Mechanisms of analogy and contextual influence**  
(Bar 2004, 2007)



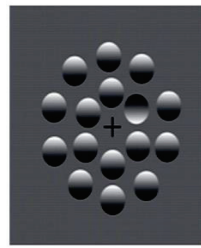
**A.** Simplified process of analogy connecting the input with known and predicted attributes. Selection of the maximal amount of feature ( $F$ ) overlapping with the input (Bar, 2007)

**B.** Context-based predictions make object recognition more efficient. The hairdryer in the top panel and the drill in the bottom panel are identical objects: contextual information uniquely resolves ambiguity in each case (Bar, 2004).

Priors or expectations can be either structural or contextual (Seriès and Seitz 2013). Structural priors correspond to default expectations based on implicit learning of the natural environment. It can explain the “*light from above*” illusion (Figure 16) in which shapes can be seen as bumps or dimples, simply based on the structural prior in our environment that sun light usually comes from above (Adams et al. 2004; Gerardin et al. 2010; Thomas et al. 2010).

However, experimental evidence suggest that structural priors could be updated through experience (Adams et al. 2004).

Contextual priors can change the interpretation of an ambiguous image. For instance, depending on the context, the bistable image in Figure 16 can be seen rather as a rabbit or as a duck. Indeed, with a similar bistable image, the majority of children interrogated on Easter day interpreted this image as a rabbit, whereas a majority of children interrogated in October interpreted it as a duck (Brugger and Brugger 1993).

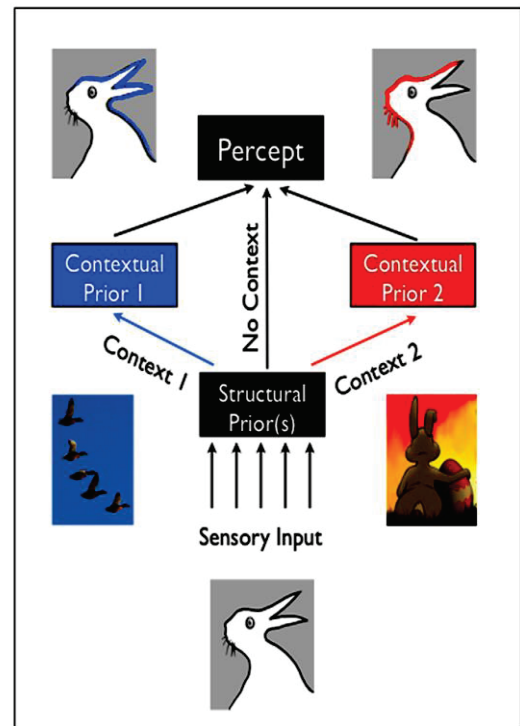


*Left: Light-from-above illusion as an example of structural prior.*

*Right: rabbit or duck bistable image, example of contextual prior.*

**Figure 16 : Structural and contextual expectations**

(Seriès and Seitz 2013)



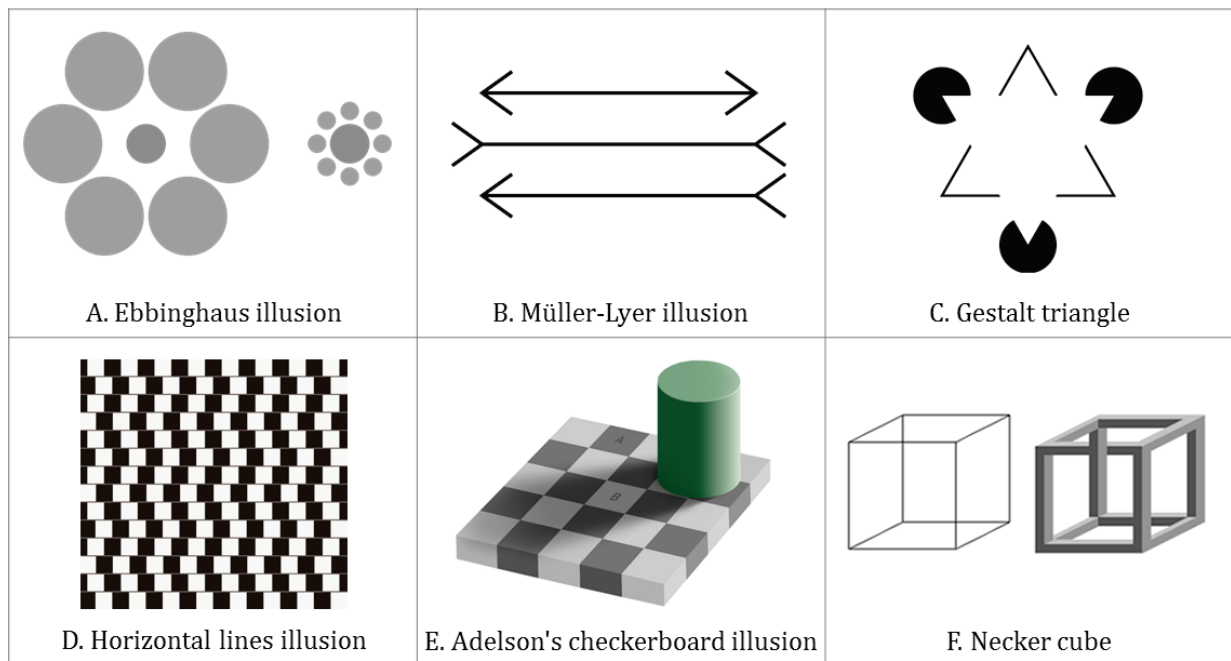
### II. 1. C. Examples of Bayesian inference tasks

The predictable features of stimuli and associated contexts can facilitate perception and stimulus recognition, but can also occasionally lead to inaccurate perception (Bar 2004, 2007). Several tasks were developed to test how our perception can be biased by priors. Bayesian inference can be experimentally tested in tasks presenting some ambiguity. It will provoke a distortion of the percepts, especially when the subjects need to take decisions from noisy sensory inputs. In these contexts, participants are going to rely on their priors to a great extent. Contextually driven expectations can bias perception (Bar 2004), which can be observed in tasks revealing misrecognition of objects belonging to the context (Palmer 1975; Bar 2004; Schlangen and Barenholtz 2015), false memories (Miller and Gazzaniga 1998; Carpenter and Schacter 2016; Devitt and Schacter 2016), or linguistic distortions (Morris and Harris 2002). These priors might have been learnt over different time scales: over a lifetime for visual illusions or over a minute for “time-order effect” tasks. These kinds of tasks are described in the following sections. The so-called time-order effect is particularly detailed, because we use this effect in several experiments of this thesis (studies III and IV).

### ***Bayesian inference in visual illusions***

In 1968, Gregory already raised the question of how the brain would manage to interpret ambiguous images (Gregory 1968). Visual illusions illustrate how our perception can be biased by prior knowledge and contextual priors. Some authors suggest that visual illusions should be considered as rational inferences with optimal computations, rather than as perceptual errors (Weiss et al. 2002). Examples of common visual illusions are shown in Figure 17.

**Figure 17 : Examples of visual illusions**



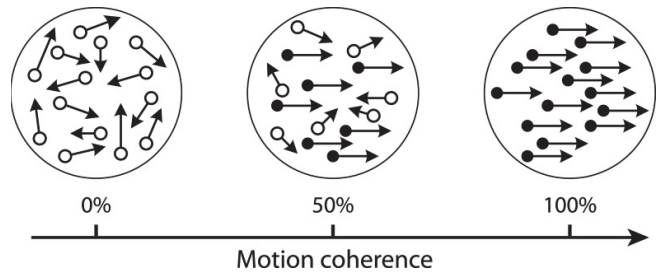
*Percepts can be biased by priors, leading to illusions of differences in size (A and B) or shades of grey (E) between similar items, to the appearance of an invisible shapes (C), of inclined lines (D), or of perspectives (F).*

For instance, in Figure 17.C (Gestalt triangle), we tend to perceive a white triangle even though the edges of the triangle are absent. Given our prior knowledge and the sensory data available, our brain infers that the most probable structure is a white triangle overlaying three black discs and another triangle with black contours. Indeed, given our previous experience of our environment, it is more parsimonious to consider a white triangle rather than six independent shapes arranged in this very specific configuration.

### ***Bayesian inference in random dot tasks***

Another way to study Bayesian inference in an ambiguous context consists in using random dot kinetograms to measure perceived motion coherence (Cornelissen et al. 1995; Barlow and Tripathy 1997; Milne et al. 2002; Dakin and Frith 2005; Zhang 2012; Manning et al. 2014). In these tasks, subjects watch an ensemble of dots, a proportion of which move along a certain direction, while the others move randomly. Subjects have to indicate the main direction of the dots. A threshold of motion coherence can be calculated as the lowest proportion of dots needed to correctly identify the global direction of the dots.

**Figure 18 : Motion coherence task (moving dots)**  
(Zhang 2012)



In these tasks, the sensory noise level can be easily adjusted by changing the percentage of dots with coherent movement, by modifying the precision of the trajectory of the dots, or by adding some variability in the direction of movement (Dakin and Frith 2005). With these ambiguous contexts, participants need to perceptually infer the main direction of the movement given the variance of the sensory information.

### ***Bayesian inference and the time-order effect***

Many of the perceptual tasks investigating the Bayesian brain hypothesis make use of effects such as the contraction bias described by Hollingworth (1910). A contraction bias is observed when the magnitude of a feature is over or underestimated, so that it is perceived as closer to the average magnitude than it actually is (Hollingworth 1910).

A kind of contraction bias is observed in two alternative forced choice tasks where two stimuli are successively presented. This observed bias is usually referred to as the “time-order effect” (TOE). Participants have to compare the magnitude of a given feature between the two stimuli. Depending on the order of presentation, the difference in magnitude between the two stimuli will either be perceived as diminished or amplified (Preuschhof et al. 2010; Ashourian and Loewenstein 2011; Englund and Hellström 2012; Karim et al. 2013; Hellström and Rammsayer 2015). Hence, the comparison of the two stimuli will seem to be harder or easier. The time-order effect operates as if an implicit prior encoding the average magnitude of the feature would bias the subject decisions.

Interestingly, priors do not need to be lifetime learnt priors, but can be manipulated in an experimental design to be learnt over a few minutes only (Jazayeri and Shadlen 2010; Preuschhof et al. 2010; Ashourian and Loewenstein 2011).

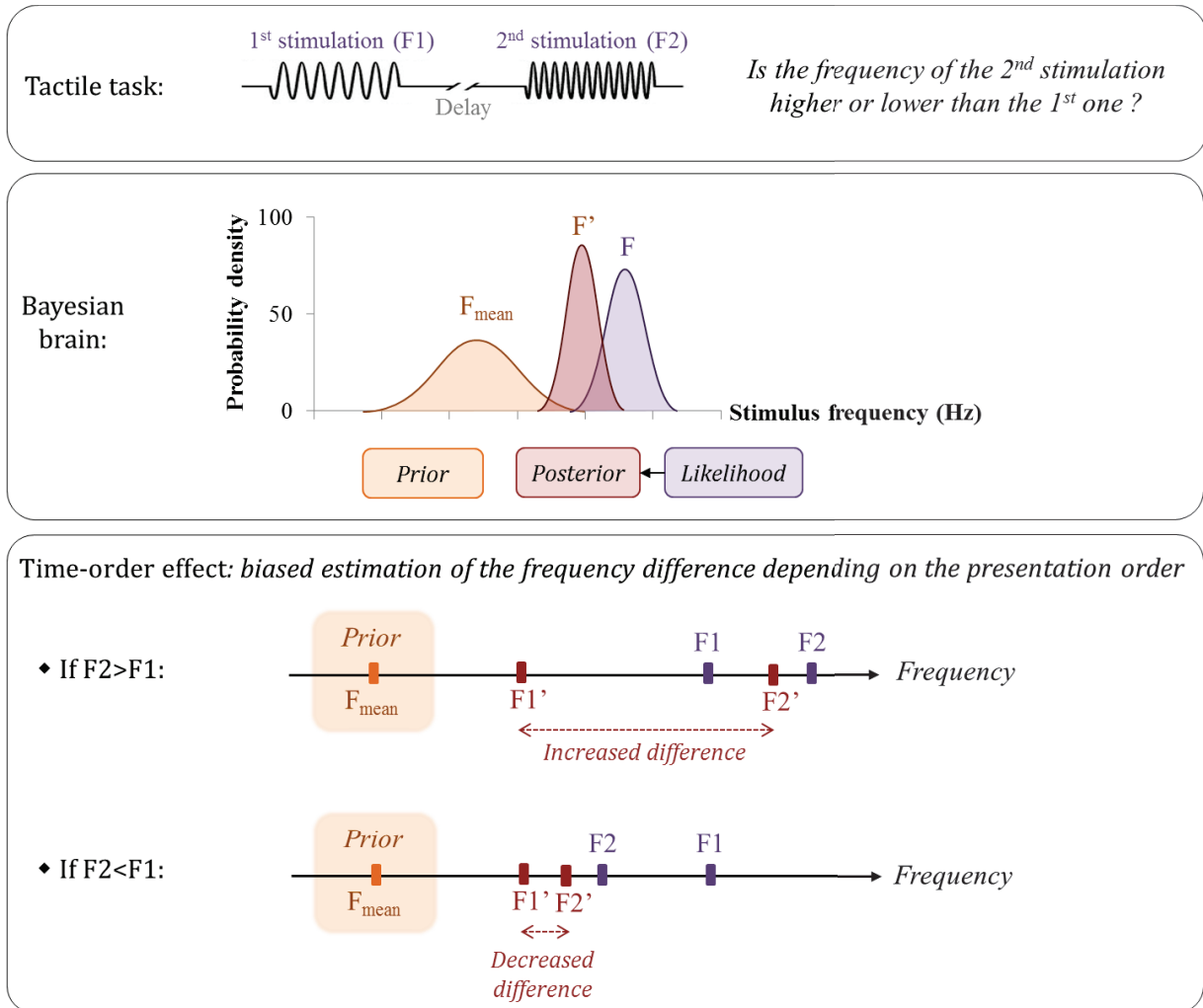
Time-order effects have been evidenced in many features of visual, auditory and tactile modalities as well as in temporal interval judgment tasks (Romo et al. 2000; Jazayeri and Shadlen 2010; Preuschhof et al. 2010; Ashourian and Loewenstein 2011; Englund and Hellström 2012; Karim et al. 2013; Wiener et al. 2014; Hellström and Rammsayer 2015).

The time-order effect was previously described in several tasks investigating tactile perception in human and non-human primates (Karim et al. 2013; Preuschhof et al. 2006, 2010; Romo et al. 2000; Sinclair and Burton 1996). In these tasks, participants receive two successive vibrations, and have to determine whether the frequency of the second stimulation is higher or lower than the frequency of the first one. During the task, subjects implicitly build-up a prior on the forthcoming frequency of stimulation, centered on the mean frequency of the previously perceived stimulations. Such a design results in a perceptual bias: the first stimulation (to be memorized) is underestimated when it is larger than the average of the delivered frequencies; and is overestimated when smaller. Figure 19 illustrates how perception is biased toward priors in a frequency comparison task involving two successive tactile stimulations.

The TOE would be due to a larger contribution of the prior to the perception of the first stimulus, compared to the one of the second stimulus. It has been suggested that this difference in contribution emerges from the delay (memorization) period which follows the first stimulation. Preuschhof et al. (2010) found that the TOE increased when the inter-stimuli interval (ISI) increased (100ms vs 4100ms). This result suggests that the delay between the two stimuli increases uncertainty about the first stimulation, augmenting the relative weight of prior information on the perception of the first stimulation. Nonetheless, Karim et al. (2013) found a stronger TOE for shorter ISI (300ms) in a vibrotactile discrimination task. They observed a complex non-linear dependence between the size of the TOE and the ISI (testing four delays: from 300 to 2400ms) (Karim et al. 2013).

Hence, the time-order effect can show how *posteriors* are computed from the *likelihood* and *prior* distributions, whose relative weight depend on the precision of these distributions.

**Figure 19 : Time-order effect in a vibrotactile frequency discrimination task**



In this task, subjects receive two successive tactile stimulations on their finger, and are asked to compare their frequencies. Percepts of the 1<sup>st</sup> and 2<sup>nd</sup> stimulations are shifted toward the *prior* ( $F_{\text{mean}}$ ). The percept of the 1<sup>st</sup> stimulation is even more shifted toward the *prior* because the delay period might decrease the weight of the sensory evidence relatively to the prior weight.

**F1:** 1<sup>st</sup> stimulation, **F1'**: F1 posterior mean.

**F2:** 2<sup>nd</sup> stimulation, **F2'**: F2 posterior mean.

In the case where frequencies are higher than the prior  $F_{\text{mean}}$ , the perceptual bias is the following:

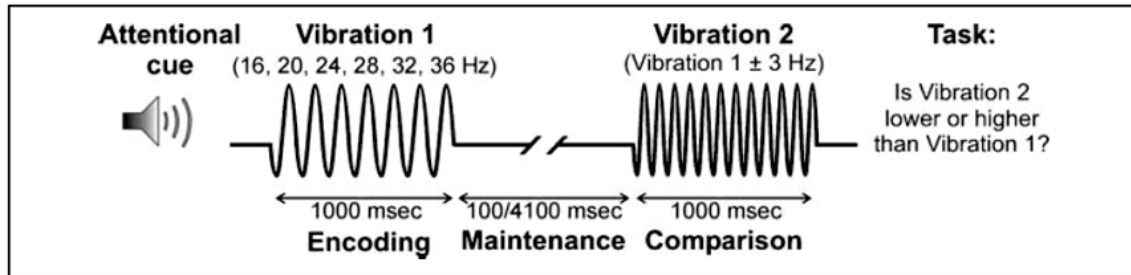
- ◆ If the 2<sup>nd</sup> frequency is higher than the 1<sup>st</sup> one ( $F_2 > F_1$ ):
  - ▷ The difference between the percepts  $F_1'$  and  $F_2'$  will be perceived as increased, resulting in a facilitated comparison of the frequencies.
- ◆ If the 2<sup>nd</sup> frequency is lower than the 1<sup>st</sup> one ( $F_2 < F_1$ ):
  - ▷ The difference between the percepts  $F_1'$  and  $F_2'$  will be perceived as decreased, resulting in a harder comparison of the frequencies.

The time-order effect expresses in the accuracy and speed of responses. Figure 20 shows the results from a tactile discrimination task eliciting a time-order effect (Preuschhof et al. 2010). For frequencies higher than the expected frequency, accuracy is higher and

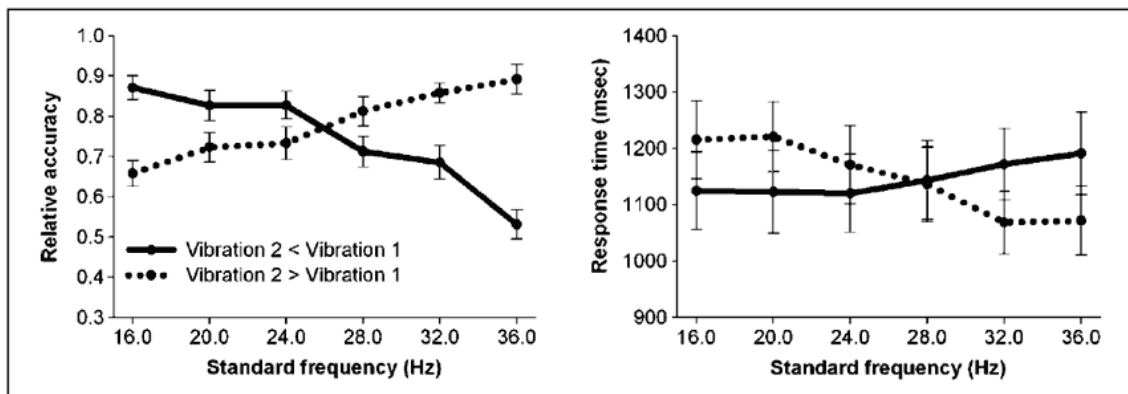
response times shorter when the 2<sup>nd</sup> frequency is higher than the 1<sup>st</sup> one (i.e., further away from the prior frequency), whereas accuracy is worse and response times longer when the 2<sup>nd</sup> frequency is lower than the 1<sup>st</sup> one. For frequencies lower frequency than the expected frequency, the reverse pattern is found.

**Figure 20 : Results from a tactile time-order effect task**  
(Preuschhof et al. 2010)

A. Experimental design



B. Time-order effect on performance (left) and response times (right)



The TOE is centered on the prior, corresponding to the mean value of the feature studied. A shift in the prior distribution results in a similar translational shift in the bias curve (Ashourian and Loewenstein 2011).

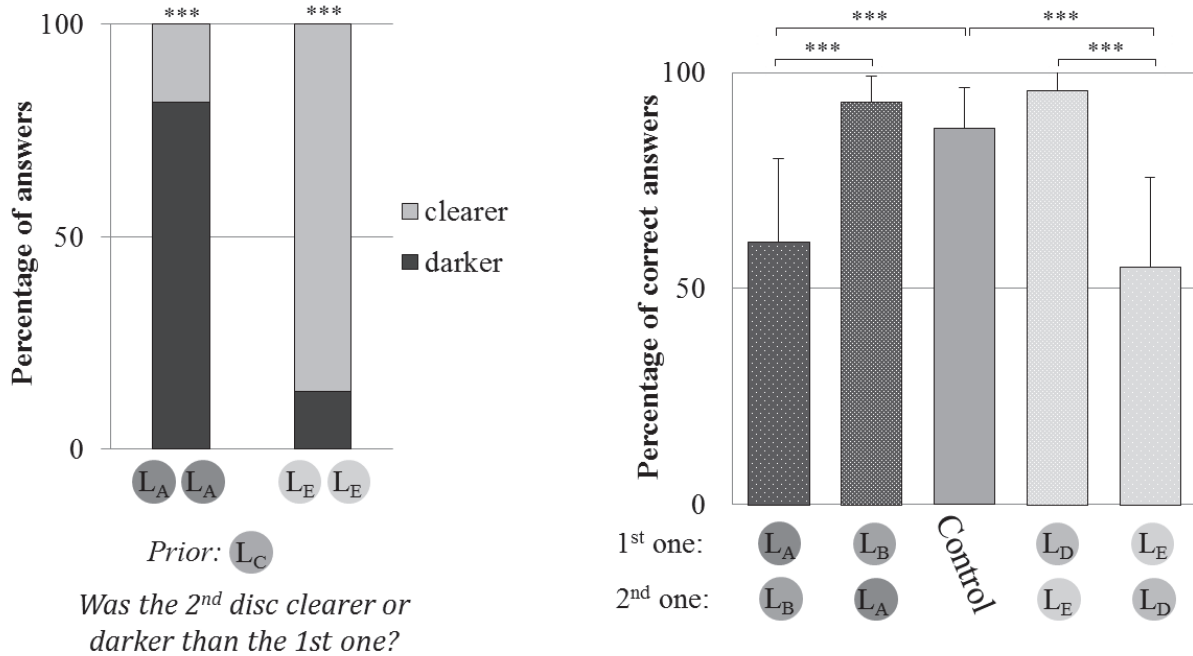
*Pilot study of a visual time-order effect*

In a pilot study with 24 control participants, we investigated the time-order effect in a visual task. In this task, participants had to compare the luminance of two successively displayed discs. Participants were asked to determine whether the 2<sup>nd</sup> disc was clearer or darker than the 1<sup>st</sup> one. There were five possible degrees of luminance for the discs, the darkest luminance being  $L_A$ , the average  $L_C$  and the clearest  $L_E$ . The complete description of



this task (methods and results) is available as Supplementary material (Appendix 1). The main findings are presented in Figure 21.

**Figure 21 : Pilot study on a visual time-order effect in controls**



**Left:** Percentage of answers “clearer” and “darker” when two similar discs were successively shown (darker ones: L<sub>A</sub>, clearer ones: L<sub>E</sub>). The prior on the luminance is L<sub>C</sub> corresponding to the average luminance displayed.

\*\*\*  $p < 10^{-4}$ ; percentage of answers “clearer” and “darker” significantly different from chance level.

**Right:** Percentage of correct answers when two discs of different luminance were successively shown. Accuracy highly depended on the order of presentation of the luminance.

The percentage of correct answers is near chance level for the presentation of L<sub>A</sub> followed by L<sub>B</sub>, and for L<sub>E</sub> followed by L<sub>D</sub>.

As a contrary, accuracy is improved when L<sub>B</sub> is followed by L<sub>A</sub>, and when L<sub>D</sub> is followed by L<sub>E</sub>.

The control condition corresponds to the cases where the 1<sup>st</sup> stimulus is L<sub>C</sub> (the prior).

More details are available in the Appendix 1 of the supplementary material. \*\*\*  $p < .001$

The TOE could be seen for two discs of different luminance (right graphic), but also for two discs of similar luminance (left graphic).

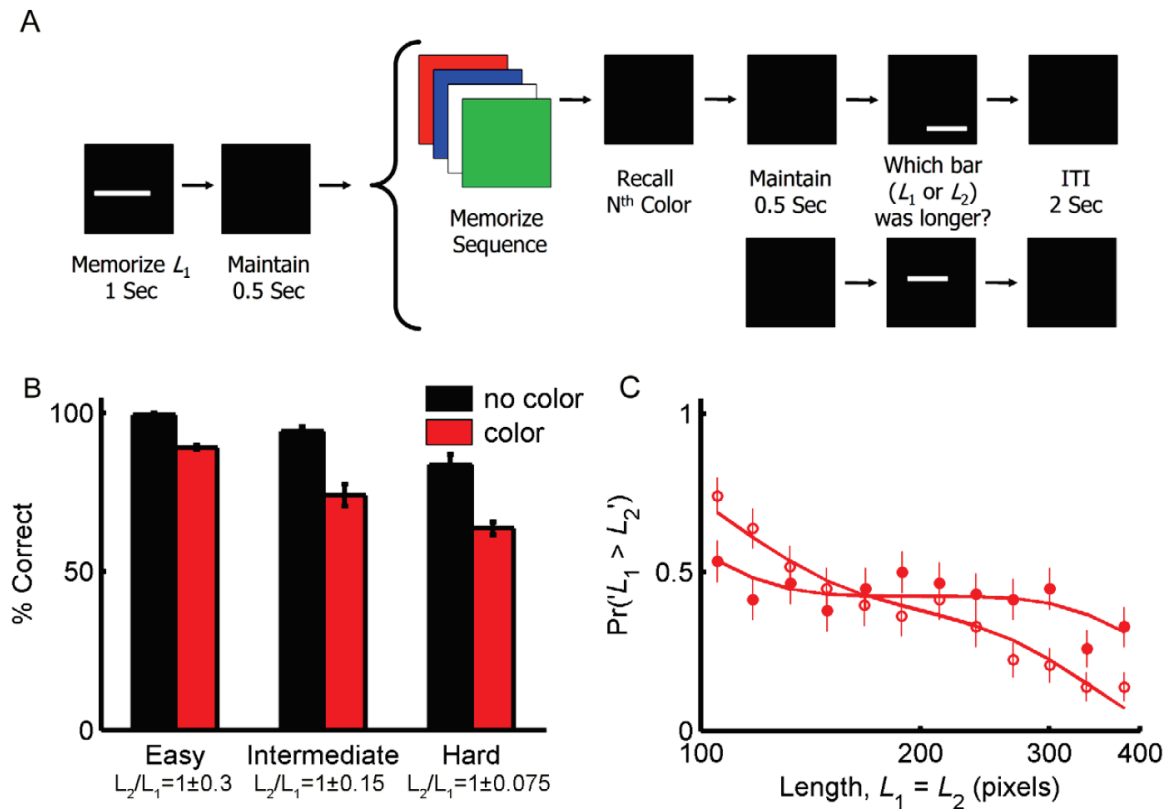
When two dark discs are successively presented (L<sub>A</sub>), the percept of the 1<sup>st</sup> disc will be drifted toward the prior (L<sub>C</sub>) to a greater extent than the 2<sup>nd</sup> one. Then, the 2<sup>nd</sup> disc will be perceived as darker than the 1<sup>st</sup> one (as the prior L<sub>C</sub> is clearer than L<sub>A</sub>).

When two discs of different luminance are presented, the comparison of L<sub>B</sub> followed by L<sub>A</sub> seems facilitated, because L<sub>B</sub> is clearer than L<sub>A</sub> and is drifted toward the clearer prior L<sub>C</sub>. As a contrary, when L<sub>A</sub> is presented before L<sub>B</sub>, the comparison seems harder, because L<sub>A</sub> is darker than L<sub>B</sub>, but is drifted toward the clearer prior L<sub>C</sub>.

*Effect of noise on the time-order effect*

Ashourian and Loewenstein (2011) investigated how the time-order effect evolves when noise is added to the representation of the first stimulus. They used a TOE task where participants had to compare the length of two horizontal bars successively displayed. In order to blur the representation of the first stimulus, they added a distracting memory task between the presentations of the two bars, where subjects had to memorize a series of flashing colors on the screen. Adding such noise in the representation of the first stimulus increased the size of the TOE (Ashourian and Loewenstein 2011). These results are shown in Figure 22.

**Figure 22 : Effect of noise on the time-order effect**  
(Ashourian and Loewenstein 2011)



**A.** Task design: half of the trials were a classical TOE task (standard version), and the other half included a distraction memory task (color version).  $L_1/L_2$ : Length of the first/second bar.

**B.** Percentage of correct answers in the bar length comparison in the standard (black) and color (red) tasks. Results are shown for easy trials ( $\pm 30\%$  of difference between  $L_1$  and  $L_2$ ), intermediate trials ( $\pm 15\%$  of difference) and hard trials ( $\pm 7.5\%$  of difference).

**C.** Response curve in the standard (filled circles) and color trials (open circles). The larger slope of the response curve on the color trials compared to the standard trials suggests that the secondary task caused an enhancement of the contraction bias. Lines are the best fit of the Bayesian model.

These results suggested that the contraction bias, leading to the TOE, occurred during decision making and not during memory encoding of the stimulus (Ashourian and

Loewenstein 2011). The extent of the bias depended on the precision of the memory of the sensory input.

### *II. 1. D. From Bayesian brain theories to ASD*

As the Bayesian brain theory was successful in explaining how our perception of the world emerges, recent theories were formulated to explain the atypical perception in ASD (Brock 2012; Pellicano and Burr 2012; Van de Cruys et al. 2013, 2014; Lawson et al. 2014). These theories mostly rely on autistic symptoms such as atypical sensory processing, intolerance to change and atypical learning. They intend to explain both social and non-social symptoms of ASD.

The Bayesian approach applied to psychiatry led to the emergence of computational psychiatry, which could help understanding this spectrum of disorders (Montague et al. 2012; Stephan and Mathys 2014). First, a Bayesian approach of ASD proposes a unifying view of ASD, encompassing sensitivity and perceptual issues, as well as social comprehension difficulties. In addition, Bayesian brain theories of ASD might contribute to the improvement of the diagnosis and treatment of individuals with ASD (Haker et al. 2016). The diagnosis of psychiatric disorders can hardly be made through direct access to tissues or biomarkers, and so, hidden causes cannot be inferred, as opposed to many diseases. Computational models based on generative models of behavioral or cerebral activity could infer these causes (Stephan and Mathys 2014). As maladaptive cognition is characterized by aberrant learning and inference, investigating priors, prediction errors and precision of sensory inputs can help understanding many psychiatric disorders (Stephan and Mathys 2014; Haker et al. 2016).

In ASD, many symptoms point to an imbalance in the regulation of the precision of one of these three elements (Brock 2012; Pellicano and Burr 2012; Van de Cruys et al. 2013, 2014; Lawson et al. 2014; Sinha et al. 2014; Friston 2016). Indeed, the difficulties to generalize or have abstract representations of either sensory inputs or language suggest atypical priors. Rituals and the need to exert control can be seen as ways to minimize prediction errors. Difficulties linked to unexpected changes and surprises might suggest atypical prediction errors in ASD. Considering ASD in the Bayesian brain framework could have consequences on possible behavioral therapies, by giving keys on the necessity to establish a predictable environment, or to give explicit definitions of abstract concepts rather than waiting for intuitive buildup (Haker et al. 2016).

Figure 23 summarizes the section II.1 on Bayesian brain.

*Figure 23 : Summary of part II.1*

## II.1. The Bayesian brain

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19<sup>th</sup> & early 20<sup>th</sup> century:

- ◆ von Helmholtz ▷ Unconscious inference by the brain
- ◆ Hollingworth ▷ Central tendency of Judgement & contraction bias

**Bayesian inference:** ▷ Percepts (*posteriors*) result from the (optimal) combination of incoming information (*likelihood*) and inner predictions (*priors*)

```
graph TD; P[Prior] <--> L[Likelihood]; P --> Post[Posterior]; L --> Post; PE[Prediction error]; PE --- PE_text[To be minimized];
```

▷ Percepts drifted toward *priors*

*Observed in visual illusions, random dot tasks, with the time-order effect ...*

▷ Importance of the balance of *prior* and *likelihood* precisions

## II. 2. Bayesian accounts of ASD

Bayesian brain theories of ASD suggest weaker priors, higher sensory confidence, and more globally, an imbalance in the relative precision of priors and sensory inputs, leading to highly precise prediction errors.

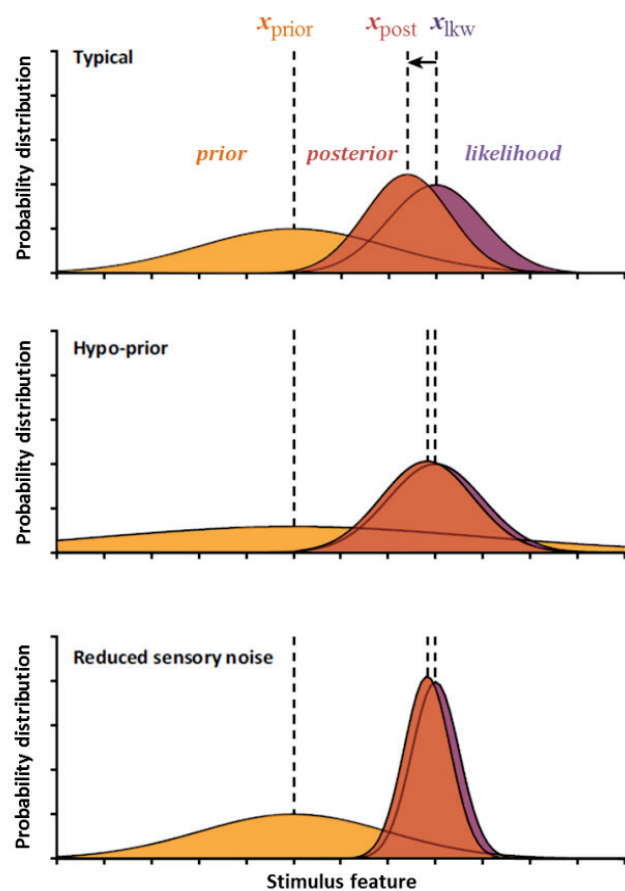
### II. 2. A. Decreased precision of priors in ASD?

Pellicano and Burr (2012) were the first to propose a Bayesian explanation of autistic perception. In their view, individuals with ASD would have a perception of their environment that is “*too real*”, as compared to NT. They suggested that this very realistic and accurate perception of the world would be due to a perception being less biased toward priors.

Pellicano and Burr (2012) argue that the WCC and EFP theories (Happé and Frith 2006b; Mottron et al. 2006) take into account the atypical autistic perception, but do not fully specify the underlying computational mechanisms, and do not explain all sensory abnormalities (hyper- and hyposensitivity, sensory seeking behaviors). In addition, they argue that previous theories need refinements in order to explain why autistic individuals have difficulties dealing with the unpredictable nature of external events.

The authors suggest that subjects with ASD have “*hypo-priors*”, corresponding to priors with large variance (Figure 24 : Bayesian . These hypo-priors should distort the sensory information to a fewer extent than in NT. This could explain their superior performance in copying impossible figures (Mottron et al. 1999) and the reduced susceptibility to illusions in ASD (Happé 1996; Mitchell et al. 2010). However, depending on the type of visual illusion, individuals with ASD might indeed show decreased susceptibility or

**Figure 24 : Bayesian theories of ASD**  
(modified from Brock 2012)



similar susceptibility as controls (see Palmer et al. 2017, for a review). In addition, the hypo-prior hypothesis is consistent with the finding that individuals with ASD are less influenced by prior knowledge in judging shapes in a context where perspective cues were removed (Ropar and Mitchell 2002). Contrary to typically developing children, children with ASD would not be helped by prior knowledge on shadows to identify objects (Becchio et al. 2010).

Concerning the autistic sensitivity, the hypo-priors could lead to experiences of sensory overload as the incoming sensory inputs would be poorly anticipated. The authors also suggest that facing changes or unexpectedness could be disadvantageous in situations where they have even less specific priors (Pellicano and Burr 2012).

Van Boxtel and Lu (2013) underlined that the predictive coding framework offers a natural implementation of the *hypo-prior* hypothesis, taking into account several levels of cortical hierarchy. They also highlighted that less precise predictions would increase prediction error, resulting in a constant bombarding by new surprises. Interestingly, within the predictive coding framework, ASD could be characterized by a “*failure of beliefs about beliefs*”, which means that there might be a wrong adjustment of the hyper-parameter controlling prior precision, as a function of contextual uncertainty (Friston et al. 2013).

In a recent study, Pellicano’s research group investigated the central judgment effect in a temporal reproduction task with children with ASD (Karaminis et al. 2016). They found that the ASD group showed a greater central tendency effect and poorer perceptual thresholds than matched typically developing children. They suggested that children with ASD did not increase enough the relative weight of their priors to compensate for their lower encoding precision. They concluded that children with ASD do not use prior knowledge to optimally reduce errors, as opposed to typically developing children. Nevertheless, their conclusion suggesting that ASD children use less prior information, therefore supporting their hypo-prior hypothesis, needs to be taken cautiously. Actually, the reduced relative influence of prior in children with ASD was only revealed when correcting the behavioral findings by accounting for individual poor temporal resolution (temporal resolution referred to their abilities to compare time intervals in series of three flashes appearing at different time distances). A main limitation of this study is that the assessment of the time interval reproduction task only relied on the precise timing of the motor responses of children with ASD, despite impaired motor abilities in children with ASD (Schmitz et al. 2003; Green et al. 2009; Fournier, Hass, et al. 2010; Gowen and Hamilton 2013).

*Evidence against the hypo-prior hypothesis*

The experiments investigating priors in individuals with ASD showed mixed results suggesting either a decreased precision (Karaminis et al. 2016), an intact precision (Ego et al. 2016; Pell et al. 2016) or an increased precision of the priors (Gonzalez-Gadea et al. 2015). An EEG study revealed a reduced response to unexpected events in the superior frontal cortex and an increased response to expected events in the dorsolateral prefrontal cortex in children with ASD, as compared to controls (Gonzalez-Gadea et al. 2015). The authors suggest that expectation abnormalities in ASD could be due to disproportionate precision allocated to priors.

A behavioral experiment investigating whether noise added to the eyes would create a perceptual bias (in which gaze would be perceived as direct) revealed no group differences between NT and ASD (Pell et al. 2016). They concluded that in this context, priors influence was intact in ASD. Moreover, adults with ASD were able to perceptually average information about a set of visual objects, suggesting an automatic form of statistical processing, including the buildup of a prior (Corbett et al. 2016). Another study investigated predictions in a blanking paradigm with adolescents with ASD (Ego et al. 2016). In this task, participants had to visually follow a moving target that sometimes disappeared. They found that both groups had similar predictive eye movements, suggesting intact predictive abilities for low-level sensorimotor transformations in adolescents with ASD.

Van de Cruys et al. (2013) highlighted that the hypo-prior hypothesis can be contested by the fact that people with ASD appear to be able to build up strong priors. Indeed, mismatch negativity (MMN) studies measure the difference between responses evoked by frequent (standard) and rare (deviant) stimuli, respectively. The MMN thus provides a measure of surprise or prediction error. ASD subjects do show a MMN response, which was proven even faster compared to controls (Gomot et al. 2002, 2008; Ferri et al. 2003; Kujala et al. 2007; Cléry et al. 2013). The small violations of the predictions led to great PE, suggesting that people with ASD indeed entertain precise priors.

*II. 2. B. Increased sensory precision in ASD?*

Following the hypo-prior hypothesis by Pellicano and Burr (2012), Brock commented on the idea that an increased precision of sensory inputs could lead to similar peculiarities of perception (Brock 2012). This is straightforward when considering Bayes theorem and the

emergence of percepts as predicted by equations 7 and 8. This indetermination or ambiguity between the effect of prior and sensory precisions is inherent to Bayes theorem and is illustrated in Figure 24. In ASD, perception could be very realistic (i.e. *posteriors* being very close to sensory evidence) either because of reduced top-down priors, or because of increased bottom-up sensory evidence. Indeed, these changes in variance would result in similar posterior means  $x_{post}$ . However, the *posterior* precision will be increased if the *likelihood* precision is increased, contrary to the reverse effect of hypo-priors. Given the heterogeneity of symptoms between ASD individuals, it might be that both mechanisms can be found in the ASD population. Brock (2012) suggested that the reduced long-range connectivity in ASD could lead to hypo-priors, while increased lateral inhibition could increase sensory precision.

Theories of ASD have suggested either an increased sensory noise (Simmons et al. 2007) or a reduced one (Davis and Plaisted-Grant 2015). A reduced sensory noise would be coherent with a more precise encoding of the sensory inputs. Note that a reduced sensory noise predicts a decreased variance in intra-individual perceptual responses to identical stimuli (van Boxtel and Lu 2013), but this kind of evidence is still lacking.

### II. 2. C. *Atypical precision of prediction errors in ASD?*

As changes in the precision of both priors and sensory input lead to similar percepts, Lawson et al. (2014) highlighted the importance of the precision balance account of ASD. They suggested that autistic behaviors may “*lie in the delicate balance of precision ascribed to sensory evidence relative to prior beliefs*”. Autistic symptoms would thus emerge from atypical precision-weighting between ascending prediction errors and descending predictions (Lawson et al. 2014; Friston 2016). Interestingly, an EEG study suggested that adults with ASD could not flexibly modulate cortical activity according to changing levels of uncertainty (Thillay et al. 2016). A recent review article proposes that ASD would be characterized by a greater weighting of prediction error, yielding an increased learning rate (Palmer et al. 2017).

#### ***The HIPPEA hypothesis***

Van de Cruys and colleagues introduced the inflexible precision of prediction errors in autism (HIPPEA) (Van de Cruys et al. 2014). This hypothesis postulates that ASD symptoms would be due to an impaired adjustment of precisions: the weighting of prediction errors would systematically remain high. Such a precise PE would result in very specific predictions. In other words, every sensory input would be learnt as novelty, therefore promoting a too



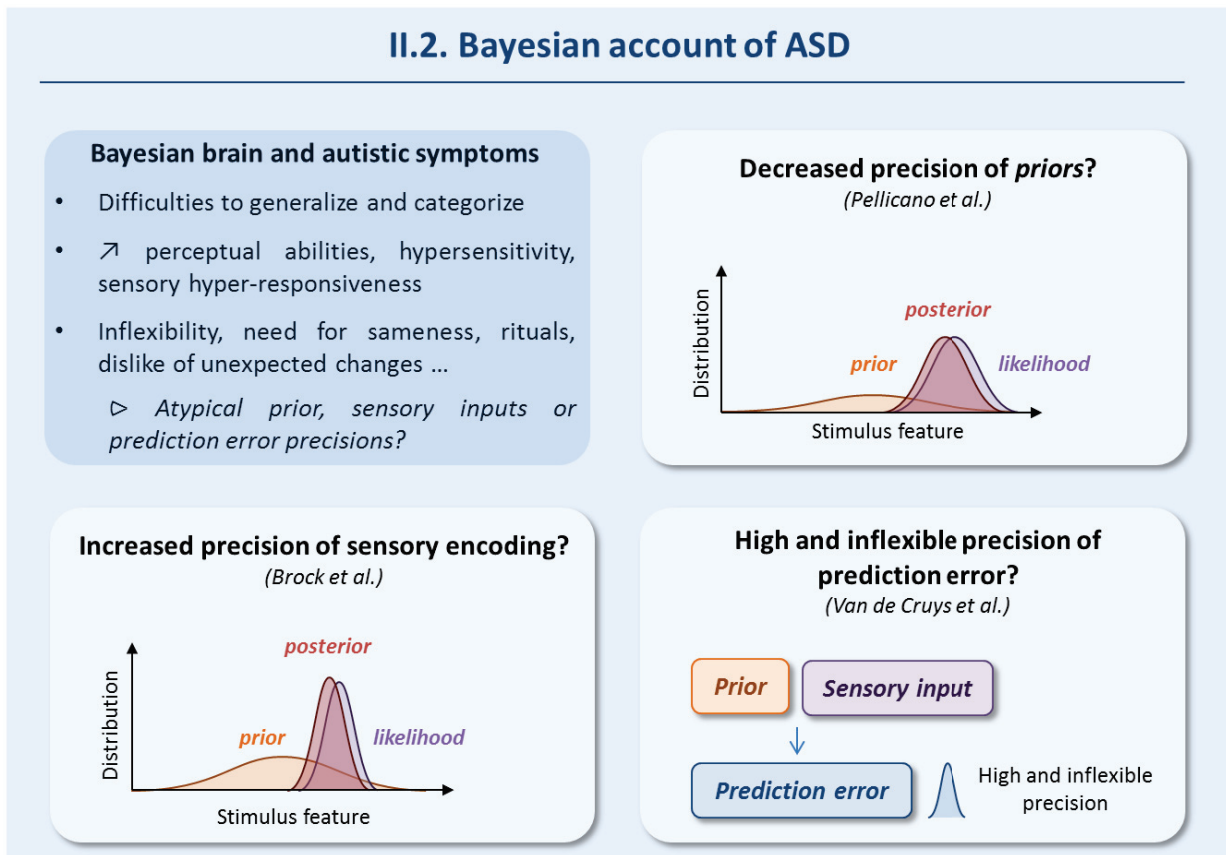
complex model of the world, prone to overfitting in certain contexts. Indeed, too precise priors hardly generalize and are thus barely applicable, since it is very unlikely that the exact same situation will repeat in the future (Van de Cruys et al. 2013). In noisy and complex environments, excessive learning would be suboptimal and would lead to “too” strong predictions. In control subjects, depending on the context, the precision of the PE can be flexibly down-regulated, so that the general rule is not systematically violated and irrelevant sensory signals are not necessarily explained away. This is in line with the idea and supporting findings that in ASD, sensory related precision weighting would not be flexibly adjusted as requested by the volatility of the context (Robic et al. 2014; Palmer et al. 2017).

The hypothesis of a high and inflexible PE precision in ASD could explain both improved and impaired autistic abilities. In rare situations, there might be an exact match between the prior and the sensory data, enabling peak abilities such as better pattern detection with less inference from other patterns which look alike (Plaisted et al. 1998; Qian and Lipkin 2011; Mottron et al. 2013). Nonetheless, in our quite complex and changing environment, the lack of generalizable inference could impair the understanding of stimuli and explain sensory overload in ASD. As such, the suboptimal adjustment of the relative weighting of prior knowledge and incoming sensory information would be consistent with the HIPPEA hypothesis.

The main consequences of HIPPEA include chronic unpredictability and repeated frustration in learning, leading to unusual sensory reactivity and atypical learning. Unpredictability has a clear negative impact on individuals as it induces stress, anxiety, mood problems and sensory avoidance (Miller 1981; Herry et al. 2007). A recent study assessed atypical sensory sensitivity, intolerance to uncertainty and anxiety in children with ASD, based on parental reports (Neil et al. 2016). They estimated that intolerance of uncertainty and anxiety scores explained half the variance in atypical sensory sensitivity in children with ASD (Neil et al. 2016).

Figure 25 summarizes the section II.2.

**Figure 25 : Summary of part II.2**

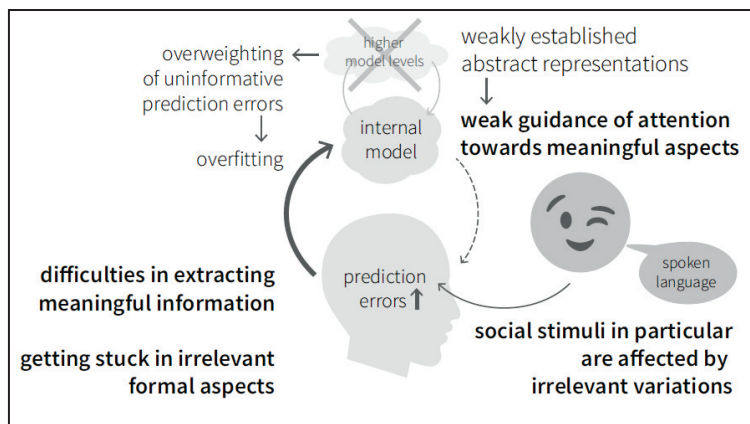


## II. 3. Psychophysiological underpinnings of aberrant precision in ASD

### II. 3. A. Behavioral correlates

#### Sensory and motor perception and learning

A schematic representation of the Bayesian brain account of autistic perception is presented below.



**Figure 26 : Bayesian brain and autistic perception**  
(Haker et al. 2016)

*Overweighted low-level prediction errors, due to overly high sensory precision, cause overfitting of the internal model and difficulties in extracting meaningful information. This impairs the establishment of high-level (abstract) representations and reduces the ability to explain away future prediction errors.*

Highly precise prediction errors generated in the lower levels of the perceptual hierarchy would yield to weaker priors in levels above. Overprecision of sensory evidence at early sensory stages of processing could lead to over-fitting priors (hyper-priors) in the lower levels of the cortical hierarchy (Van de Cruys et al. 2013), and possibly non-informative ones at higher levels of the cortical hierarchy (Van de Cruys et al. 2016). The specificity of these predictions could contribute to enhanced local and detail-oriented performance, but also to decreased global processing due to non-generalizable predictions (Dakin and Frith 2005; Happé and Frith 2006b; Mottron et al. 2009). Hence, this could explain the previously detailed difficulties found in ASD to learn global rules, categorize and generalize.

However, a recent study suggested that learning in ASD did not differ from controls (Manning et al. 2016). Participants performed a decision-making task inspired by Behrens et al. (2007) where they had to track the statistics of volatile and stable environments. In such tasks, the relative weight given to new information should depend on the environment: in a stable environment, the weighting of new sensory information should rely on the outcomes of many previous trials, whereas in unstable environments, the influence of past events should be restricted to the most recent trials. If children with ASD tend to have uniformly high and

inflexibly precise PE, the authors expected their learning rates to be increased in both stable and volatile environments as compared to controls (Manning et al. 2016). However, their results did not show any difference in learning rates between children with and without ASD (Manning et al. 2016). Yet, in a quite similar task, adults with ASD were impaired in tracking the hidden statistics in a volatile environment (Robic et al. 2014).

Constantly experiencing salient mismatch errors between the incoming sensory data and priors could easily explain hyper responsiveness and hypersensitivity encountered in ASD. In other words, sensations of sensory overwhelming can be seen as a permanent bombarding of very strong PE. However, hypo-sensitivities have also been described in ASD (Takayama et al. 2014) and remain slightly harder to explain within the HIPPEA framework. Van de Cruys et al. (2014) suggested that it could simply result from a self-protective mechanism made to escape from this constant bombarding.

Finally, sub-optimal prior learning in ASD would be highly consistent with the idea of deficits in sensorimotor representation in ASD. Indeed, it would be associated with the impaired anticipatory abilities and difficulties to understand actions found in ASD (Williams et al. 2001; Schmitz et al. 2003; Minshew et al. 2004; Rinehart et al. 2006; Brisson et al. 2012).

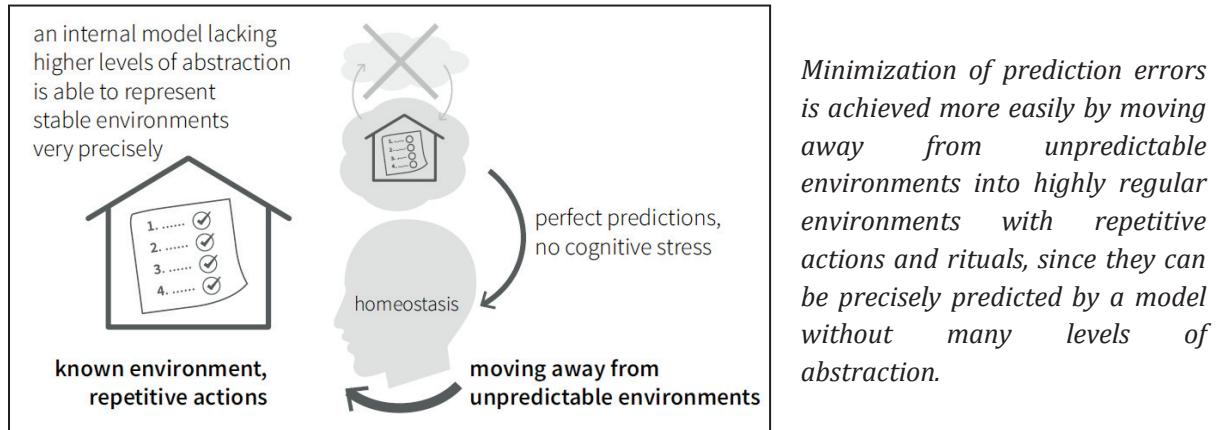
### ***Perceptual and executive flexibility***

Perceptual and executive flexibility appears to be impaired in ASD (Ciesielski and Harris 1997; Gomot and Wicker 2012; D’Cruz et al. 2013; Robic et al. 2014). Narrow priors and high prediction error precision would lead to difficulties to make flexible perceptual switches. For instance, strong predictions would reduce perceptual switching in ambiguous or bistable figures, which was shown in ASD (Ciesielski and Harris 1997; Robertson et al. 2013; Best et al. 2015). Cognitive flexibility was also shown to be reduced in ASD (Ozonoff and Jensen 1999; Kaland et al. 2008). In general, many clinical observations underlie the idea that individuals have troubles adapting to unpredictable environments (Gomot and Wicker 2012). Hence, they tend to set up a very stable and predictable environment with precise daily routine.

Repetitive behaviors are part of ASD diagnosis, and can be seen as a way to perform actions characterized by very predictable proprioceptive feedbacks. In the view of active

inference<sup>4</sup> (Friston et al. 2010, 2011), autistic repetitive and stereotyped behaviors could be abnormal but effective ways to reduce prediction errors, by experiencing well-predicted sensations. Hence, people with ASD would actively create predictability with their stereotyped actions, as a way to diminish the prediction error bombarding (Ornitz 1974; Van de Cruys et al. 2014).

**Figure 27 : Bayesian brain account of autistic repetitive behaviors**  
(Haker et al. 2016)



### **Social world**

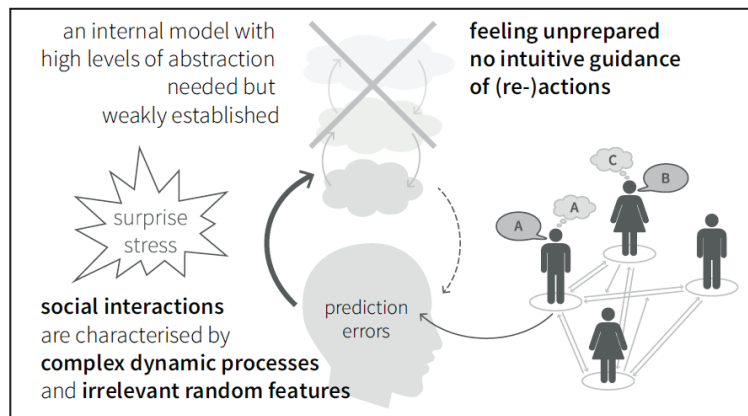
Within the Bayesian framework, social interactions can be seen as situations where subjects need to infer about others' thoughts, actions and goals, and to minimize prediction errors when they observe others' actions (Kilner et al. 2007b; Koster-Hale and Saxe 2013). Importantly, priors play a central role in disambiguating the causes of others' behaviors (Palmer et al. 2017). The interpretation of social interactions requires the combination of multiple analogies, relying on previously built priors (Bar 2009). In a point-light study, contextual information helped discriminating the communicative gestures of interacting individuals in controls, but not in adults with ASD (von der Lühne et al. 2016). This result suggested that in ASD, difficulties encountered in social interactions could be closely related to impairment of predictive coding implementation.

With noisy and fluctuating social stimuli, there is a need to ignore low-level details and to develop high-level priors enabling the comprehension of these stimuli. In ASD, having troubles inferring the meanings of facial expressions, current situations, or told stories (etc.) could lie at the heart of core difficulties in social communication and interactions.

<sup>4</sup> The concept of active inference suggests that one way to minimize prediction errors is to actively change sensory inputs to fulfill predictions (Friston et al. 2010, 2011). Indeed, in order to minimize prediction error, one can either act on its environment to make it fit its internal predictions, or flexibly change its own predictions.

Additionally, the quite unpredictable nature of social stimuli would enhance the difficulties of individuals with ASD to extract the underlying regularities of these stimuli (Robic et al. 2014). Strong prediction errors would be particularly generated with social stimuli which are very complex and show relatively high inter-individual variability.

**Figure 28 : Bayesian brain account of social interactions**  
(Haker et al. 2016)



*Social interactions are characterized by complex dynamic processes and irrelevant random features, which require suppression and regularization by an internal model with a high degree of abstraction and precise predictions. A relative failure of this model makes it difficult to infer the causes of social stimuli (i.e., understanding the meaning of social processes) and, thus, to interact with others.*

### II. 3. B. Neurophysiological correlates

The neural correlates of ascending prediction errors/sensory signals and descending predictions/priors remain quite unclear. In the predictive coding framework, predictions and prediction errors are generated at every level of the cortical hierarchy. Bell and colleagues found that the fusiform gyrus encompasses some neurons responding to the probability of a face appearing, and some others responding to the prediction errors (Bell et al. 2016). It was therefore suggested that the inferior temporal gyrus includes a subset of neurons encoding predictions and another subset encoding prediction errors. This result supports the predictive coding framework, which supposes that predictions and prediction errors pass between superficial and deeper cortical layers within each brain region.

However, some key brain regions could be associated with higher-level priors. Many studies suggest that predictions would be encoded mostly in frontal regions, and would be confronted with inputs coming from sensory regions to give rise to a prediction error (Bar et al. 2006; Summerfield et al. 2006; Sanchez 2014.; Herding et al. 2016; Sherman et al. 2016). Even though frontal regions seem important for predictions, a larger network would be involved in prior encoding. For instance, a visual task showed that regions more active with

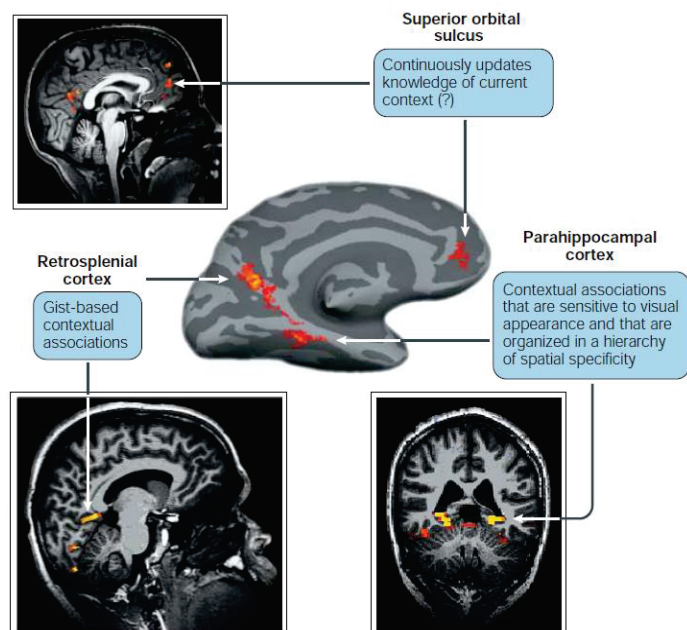
increased prior uncertainty involved the orbitofrontal cortex, the inferior frontal gyrus, the putamen, the pallidum, the amygdala, the temporal pole, the middle temporal gyrus, the posterior cingulate cortex and the insula, whereas the likelihood precision involved primary visual regions (Vilares et al. 2012).

### **Priors**

In several studies, the prefrontal cortex and inferior parietal lobe were pointed out as regions involved in contextual processing (Huettel 2005; Barcelo and Knight 2007; Gomot and Wicker 2012), uncertainty and novelty signals (Gomot et al. 2006, 2008). It was also suggested that frontal activity could reflect some adaptive adjustment of the current prediction (Schmitz et al. 2005; Schiffer and Schubotz 2011).

Within the prefrontal cortex, the most pointed out regions are the orbitofrontal cortex and the inferior frontal gyrus. In visual tasks, the orbitofrontal cortex appears to be involved in context updating (Bar and Aminoff 2003; Bar 2004; Trapp and Bar 2015) (Figure 29) and prior encoding (Sherman et al. 2016). Another key region for prior encoding would be the inferior frontal gyrus (Schmitz et al. 2005; Preuschhof et al. 2010; Spitzer et al. 2010; Sanchez 2014; Barredo et al. 2016). In particular, adjusting sensorimotor representations was associated with increased activity in the IFG (opercular part) (Schmitz et al. 2005). The IFG could also encode the precision weighted posterior probability (De Martino et al. 2013; d’Acremont et al. 2013; Sherman et al. 2016). In addition, a tactile discrimination task revealed that increased influence of expectations on perceptual decisions (between subjects) was associated with increased activity in the inferior parietal lobe and the somatosensory cortex (Preuschhof et al. 2010).

**Figure 29 : Cortical network for contextual association among visual objects**  
(Bar 2004)



### ***Prediction errors***

Prediction violations were shown to enhance firing rates, event-related potentials and BOLD responses (see Bastos et al. 2012, for a review). The neural bases of prediction errors are usually studied in the context of oddball paradigms, associative learning tasks, decision-making tasks associated with rewards or simple discrimination tasks. The main regions identified as playing a role in computing prediction errors include the anterior cingulate cortex (ACC), the dopaminergic system, the striatum, the cerebellum, the hippocampus, the prefrontal cortex, the inferior parietal lobe and the anterior insula. The ACC was one of the first regions described as involved in processing error signals and in tracking the environmental volatility (Berns et al. 1997; Schultz and Dickinson 2000; Ide et al. 2013). The cerebellum also responded to prediction errors (Courchesne and Allen 1997; Dreher and Grafman 2002).

Oddball paradigms can elicit a mismatch response, interpreted as a prediction error, when a deviant is presented after a series of standard stimuli. Mismatch negativity studies in ASD revealed atypical MMN responses to deviant stimuli, often characterized by a faster response (Gomot et al. 2002; Ferri et al. 2003; Kujala et al. 2007; Gomot et al. 2011; Cléry et al. 2013; Sokhadze et al. 2016). Models combined with experimental data suggest that the MMN reflects active cortical predictions (Garrido et al. 2009; Wacongne et al. 2012; Lieder et al. 2013a; 2013b). In the auditory modality, prediction errors involve the bilateral auditory cortex, superior temporal gyrus and prefrontal cortex (mostly IFG) (Giard et al. 1990; Doeller et al. 2003; Chennu et al. 2013; Phillips et al. 2015). In the visual modality, prediction errors involved the posterior parietal lobe, the anterior premotor cortex, the orbitofrontal cortex and the visual cortex (Pazo-Alvarez et al. 2003; Kimura 2012; Cléry et al. 2013). In the tactile modality, PE would be coordinated by the anterior insula and PE signaling would involve the IFG, inferior parietal lobe, somatosensory cortices, middle frontal gyrus, ACC, supplementary motor area, superior temporal gyrus and thalamus (Allen et al. 2016).

In visual associative learning tasks, violation of predictions were found to be associated with increased activation in the basal forebrain, substantia nigra, prefrontal regions (orbital, inferior and middle frontal gyrus), ACC, anterior insula, and inferior parietal gyrus (den Ouden et al. 2010; Iglesias et al. 2013).

Prediction errors related to movement prediction violations revealed a role of the inferior parietal lobe and IFG (Ondobaka et al. 2015) as well as the substantia nigra, hippocampus, habenula and caudate nucleus (Schiffer and Schubotz 2011; Schiffer et al.

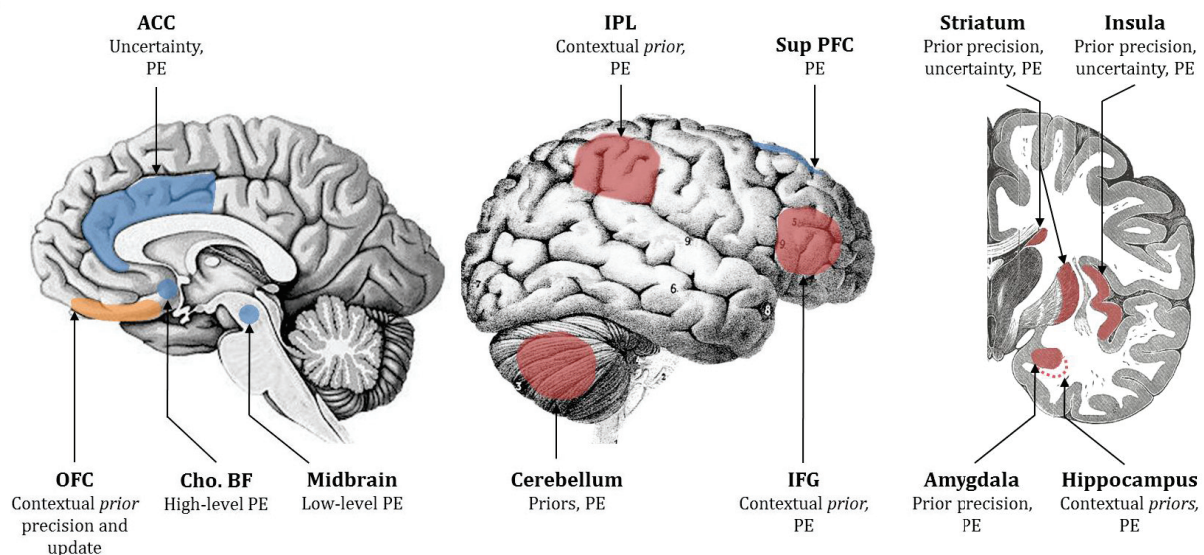


2012). Finally, in a sensorimotor task, unpredictable changes triggering prediction errors were associated with increased activity in the IFG (Schmitz et al. 2005).

Neuroimaging studies specifically designed to investigate the HIPPEA hypothesis are missing, but previous studies have investigated novelty detection in ASD. In an auditory detection paradigm, Gomot and colleagues found a widespread network for novel sounds as compared to standard, including the thalamus, STG, inferior parietal lobe, insula, cingulate, frontal regions and putamen in ASD and control groups combined together (Gomot et al. 2008). The autistic children/teenagers who performed this task recruited prefrontal and inferior parietal regions to a greater extent than controls (Gomot et al. 2008). In addition, a visual oddball task showed greater activity in the occipital cortex and in the ACC in the ASD group, as well as reduced activation in superior and middle frontal gyri, as compared to controls (Cléry et al. 2013). Likewise, a visual oddball experiment involving social and non-social targets showed greater activation in the ACC and insula in the ASD group, as compared to NT, suggesting that expectation violations were more salient in individuals with ASD (Dichter et al. 2009). However, in another study, the ACC signaled social PE in NT, but this signaling was impaired in subjects with ASD and this impairment was correlated with diagnostic measures of social deficits (Balsters et al. 2017).

Figure 30 summarizes the main brain regions supposedly involved in prediction error and prior encoding in control participants.

**Figure 30 : Brain regions potentially involved in prediction error and prior encoding**



*Illustration of the main brain regions identified in neuroimaging studies, as playing a role in prediction error (blue), priors (orange) or with mixed roles (red). Note that these regions are often task-dependent, and that predictions or prediction errors can be generated at several levels of the cortical hierarchy.*

*PE: prediction error; Cho. BF: cholinergic basal forebrain; Midbrain: dopaminergic midbrain; PFC: prefrontal cortex.*

### ***Connectivity***

Within the predictive coding framework, prediction errors pass along forward connections, while predictions pass along backward connections (Friston 2003, 2008; Kveraga et al. 2007). The precision of predictions and prediction errors would be modulated by adaptive changes in connection strengths (Friston 2008; Feldman and Friston 2010). In ASD, the difficulties to generate flexible predictions could originate from impaired top-down prediction. A verbal fluency fMRI study combined with dynamic causal modelling (DCM) showed a stronger reliance on bottom-up (stimulus-driven) connections in the ASD group, as opposed to the control group who showed a dominance of top-down connections (Radulescu et al. 2013). In addition, individuals with ASD showed greater connectivity between the ACC and sensory regions, but decreased connectivity between the ACC and the PFC and OFC, as compared to controls in a visual oddball task (Cléry et al. 2013). If high-level priors are mostly encoded in frontal regions, this could be interpreted as increased involvement of sensory inputs and decreased involvement of priors in ASD. Finally, the magnitude of social PE was driven by inputs from the ventromedial PFC in NT but not in ASD subjects (Balsters et al. 2017).

### ***II. 3. C. Molecular correlates***

Rosenberg and colleagues formulated four hypotheses to explain an increased sensory precision relatively to prior precision: (1) a narrow neural tuning function increasing sensory precision (Qian and Lipkin 2011), (2) a decreased prior precision leading to neural responses closely reflecting sensory stimuli (Pellicano and Burr 2012), (3) a reduced habituation to repeated sensory stimuli (Sinha et al. 2014), (4) a reduced inhibition from the neural population that decreases the effect of priors (Rosenberg et al. 2015). Overall, the HIPPEA hypothesis supposes that the precision of prediction error is constantly high and would not be flexibly modulated by the context.

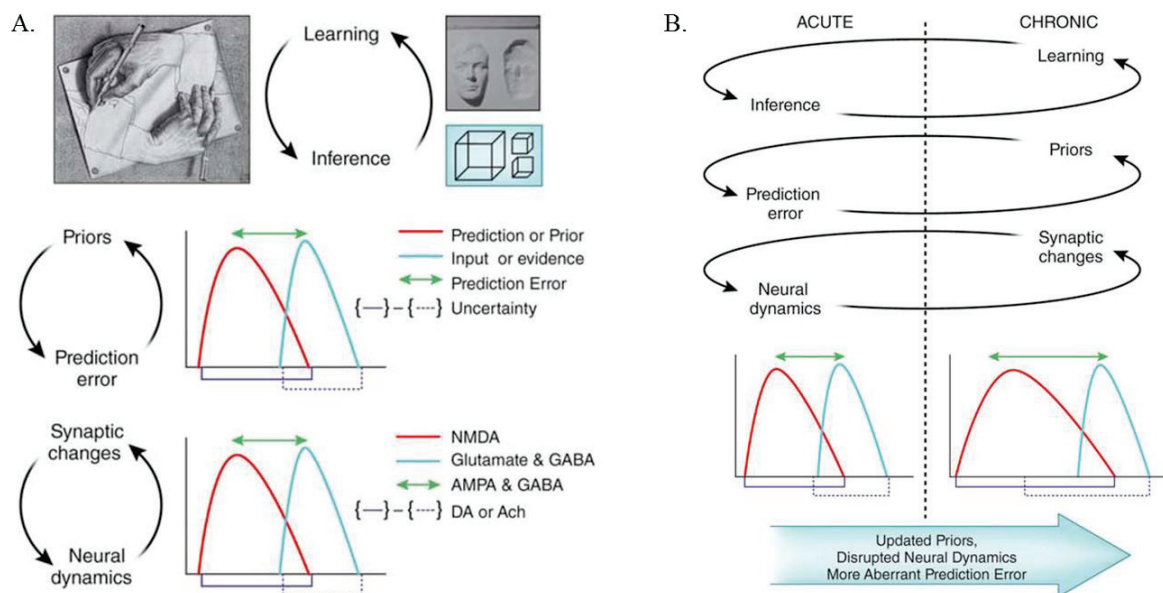
### ***Glutamate and GABA***

Hypotheses were made on the potential roles of the glutamatergic and GABAergic systems in the encoding of prediction errors (Friston 2002, 2005; Lawson et al. 2014). As NMDA glutamate receptors might play a role in gain control, abnormal functioning of the glutamatergic system in ASD could lead to failures to optimize the precision of PE (Friston

2005; Lawson et al. 2014). A recent neural network simulation showed that an increased glutamate/GABA ratio (due to decreased GABAergic inhibition) could account for the perceptual symptoms observed in ASD (Rosenberg et al. 2015). According to divisive normalization, the output of a neuron is divided by the combined excitatory and inhibitory activity of the surrounding neural population in which they are (Lawson et al. 2015; Rosenberg et al. 2015). Divisive normalization is thought to eliminate irrelevant information and to adjust the gain of neural responses. Increased divisive normalization would be consistent with a diminished plasticity in the strength of experience-dependent lateral connections between neurons, therefore reducing the influence of the context (Rosenberg et al. 2015).

Globally, rapid glutamatergic and GABAergic neurotransmission would represent prediction error *per se*, while slower neuromodulators such as acetylcholine, noradrenaline, serotonin and dopamine would modulate the precision of PE (Corlett et al. 2009, 2011) (Figure 31). The rapid glutamatergic signal might be involved in updating priors through changes in synaptic functions (Schultz and Dickinson 2000).

**Figure 31 : Model of reciprocal relationships between inference and learning, priors and prediction errors, synaptic plasticity and neural dynamics**  
(Corlett et al. 2011)



A. The authors speculate that fast neurotransmitters (GABA and glutamate) may code for the prediction error, and that slower neuromodulators (e.g., dopamine and acetylcholine, depending on the task and underlying circuitry) may compute the uncertainty.

B. Illustration of the putative effects of acute and chronic ketamine treatment within the Bayesian model. Ketamine is a glutamate inhibitor, blocking NMDA receptors. The authors predict that, with repeated ketamine exposure, aberrant learning (due to deranged synaptic plasticity) and subsequent inappropriate inferences lead to maladaptive and inaccurate representations of the world.

In addition, the precision of the incoming sensory inputs must also be modulated by the ratio between glutamate and GABA, as this ratio controls the signal to noise ratio.

As developed in section I.3.C, evidence tends to support an imbalance of glutamate and GABA in ASD, with a decreased action of the GABAergic system. In ASD, mutations found in *SHANK*, *NLGN*, and *NRXN* affect the NMDA synapses, and memantine administration, inhibiting NMDA receptors to avoid excitotoxicity, seems to improve core symptoms of ASD (Rossignol and Frye 2014).

### ***Acetylcholine and norepinephrine***

Acetylcholine and norepinephrine are two key neurotransmitters respectively mostly involved in learning and attention (Gold 2003; Hasselmo 2006). These neurotransmitters are potential candidates to control the precision of PE (Friston 2010; Lawson et al. 2014; Van de Cruys et al. 2014).

According to computational models (Yu and Dayan 2005), expected uncertainty and unexpected uncertainty are signaled by acetylcholine and norepinephrine, respectively. *Expected uncertainty* comes from known unreliability of predictive relationships within a familiar environment, whereas *unexpected uncertainty* arises from sudden changes in the environment (such as context switches) which strongly violate top-down expectations (Yu and Dayan 2005). The co-modulation of PE by acetylcholine and norepinephrine would participate in optimizing inference in a noisy and variable environment.

#### *Norepinephrine*

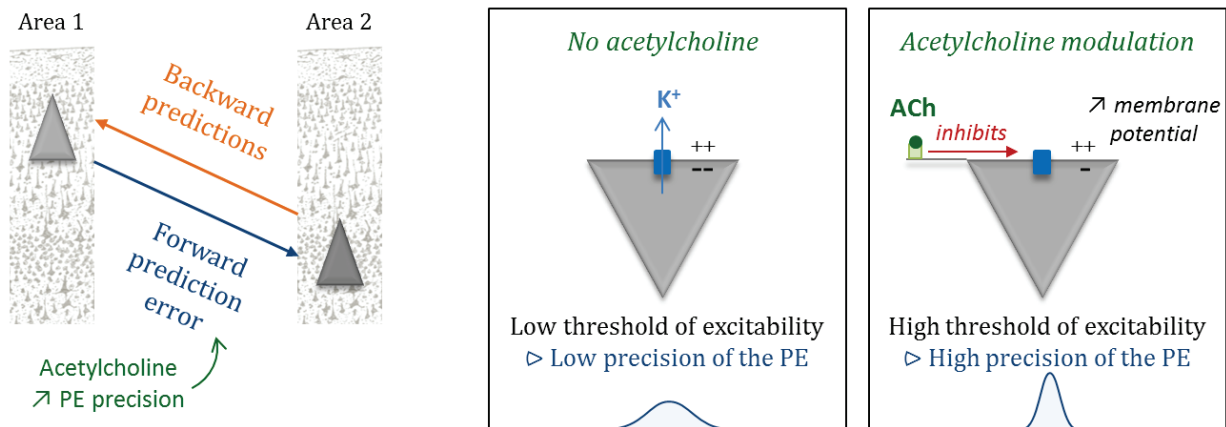
The role of norepinephrine in the modulation of PE is supported by the fact that norepinephrine neurons respond to unpredicted but not predicted rewards (Aston-Jones et al. 1997; Schultz and Dickinson 2000). An fMRI study also supported the idea that unexpected uncertainty is encoded by noradrenergic neurons of the locus coeruleus (Payzan-LeNestour et al. 2013). As the locus coeruleus is innervated by the ACC, it might contribute to modulate the gain of PE (Aston-Jones and Cohen 2005).

#### *Acetylcholine*

A pharmacological EEG study assessed the role of acetylcholine in the modulation of the precision of PE (Moran et al. 2013). They used an auditory oddball paradigm in participants who had received either a placebo or galantamine, which is an acetylcholinesterase inhibitor. With galantamine (and so, increased acetylcholine level), the amplitude of the MMN was increased in control participants. Dynamic causal modeling

showed that acetylcholine enhanced the precision of the bottom-up PE, by optimizing the gain of supragranular pyramidal cells in primary sensory cortex (Moran et al. 2013). This hypothesis is illustrated in Figure 32.

**Figure 32 : Model of a modulation of prediction error precision by acetylcholine**



This illustration presents the hypothesis of Moran et al. (2013) suggesting that acetylcholine (ACh) enhances the prediction error (PE) precision by optimizing the gain of supragranular pyramidal cells. The increased neuronal gain would be due to acetylcholine binding on muscarinic receptors. This would lead to an inhibition of calcium-dependent potassium channels, therefore facilitating neuronal depolarization. Hence, acetylcholine would enhance the neuron excitability which would enhance the precision of the prediction error.

In addition, optogenetic studies modulating the activation of neurons in the basal forebrain (the main source of acetylcholine) suggested that acetylcholine can modulate the precision of visual PE (Pinto et al. 2013). Precisely, acetylcholine would encode the precision of high-level PE (Iglesias et al. 2013).

Abnormalities in the cholinergic and noradrenergic systems were reported in ASD. They showed reductions of cholinergic receptor binding in the parietal, frontal, and cerebellar cortices (Perry et al. 2001; Lee et al. 2002), but higher concentration of brain-derived neurotrophic factor, promoting cholinergic neurons survival (Perry et al. 2001). In addition, increasing cholinergic modulation (e.g., with galantamine or donepezil) improved symptoms in ASD (Rossignol and Frye 2014). Concerning norepinephrine, results in ASD are unclear as its concentration would be increased in plasma (Lake et al. 1977; Lam et al. 2006), but not cerebrospinal fluid (Lam et al. 2006). In addition, there would be a decreased activity of the dopamine- $\beta$ -hydroxylase in ASD, which is an enzyme converting dopamine into norepinephrine, therefore suggesting less norepinephrine (Lake et al. 1977).

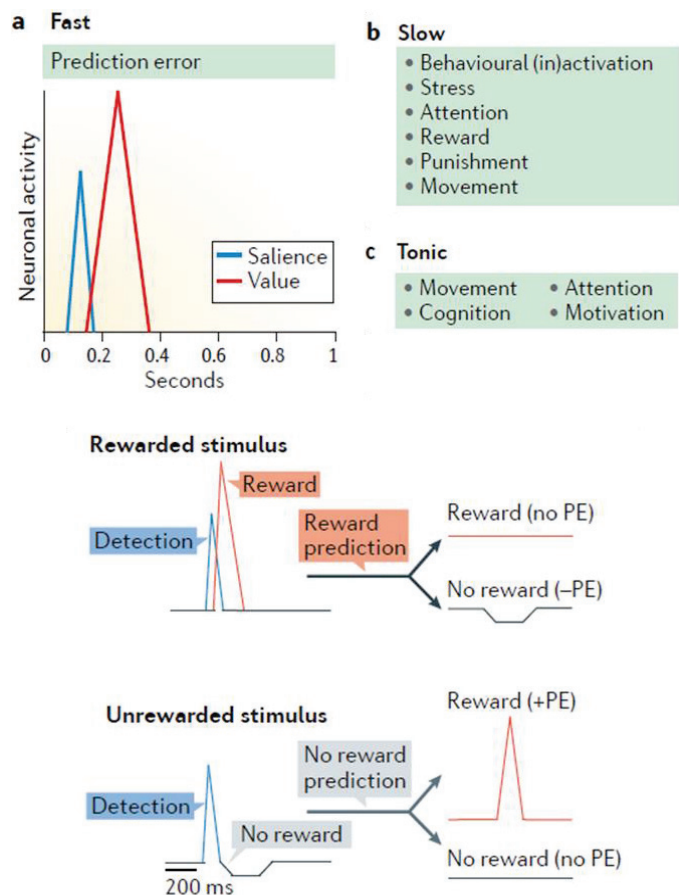
## Dopamine

Several studies have highlighted the role of dopamine in the encoding of reward PE, corresponding to the difference between received and predicted rewards (Schultz and Dickinson 2000; Steinberg et al. 2013; Eshel et al. 2016; Mathar et al. 2016; Sadacca et al. 2016; Schultz 2016a, 2016b). An optogenetic study showed that temporally precise dopamine neuron activity was sufficient to signal new cue-reward learning and to change the previously learnt cue-reward association (Steinberg et al. 2013).

Phasic dopamine discharge would encode the precision of reward PE and optimize the precision of PE in a non-reward context (Corlett et al. 2011). Schultz (2016a) proposed a two-component dopaminergic response: a brief unspecialized dopaminergic increase driven by attention, followed by a response component attributing a positive or negative value of the PE (Figure 33). More generally, single neurons recording showed that tonic discharge rates of dopamine would encode uncertainty or violation of expectations in attention-based learning tasks (Fiorillo et al. 2003; Preusschoff and Bossaerts 2007). Furthermore, the dopaminergic midbrain could modulate the precision of low-level PE (Iglesias et al. 2013).

Blood and CSF measurements of dopamine are in favor of an increased activity of dopaminergic neurons in ASD (Lam et al. 2006).

**Figure 33 : Model of prediction error modulation by dopamine**  
(Schultz 2016a)



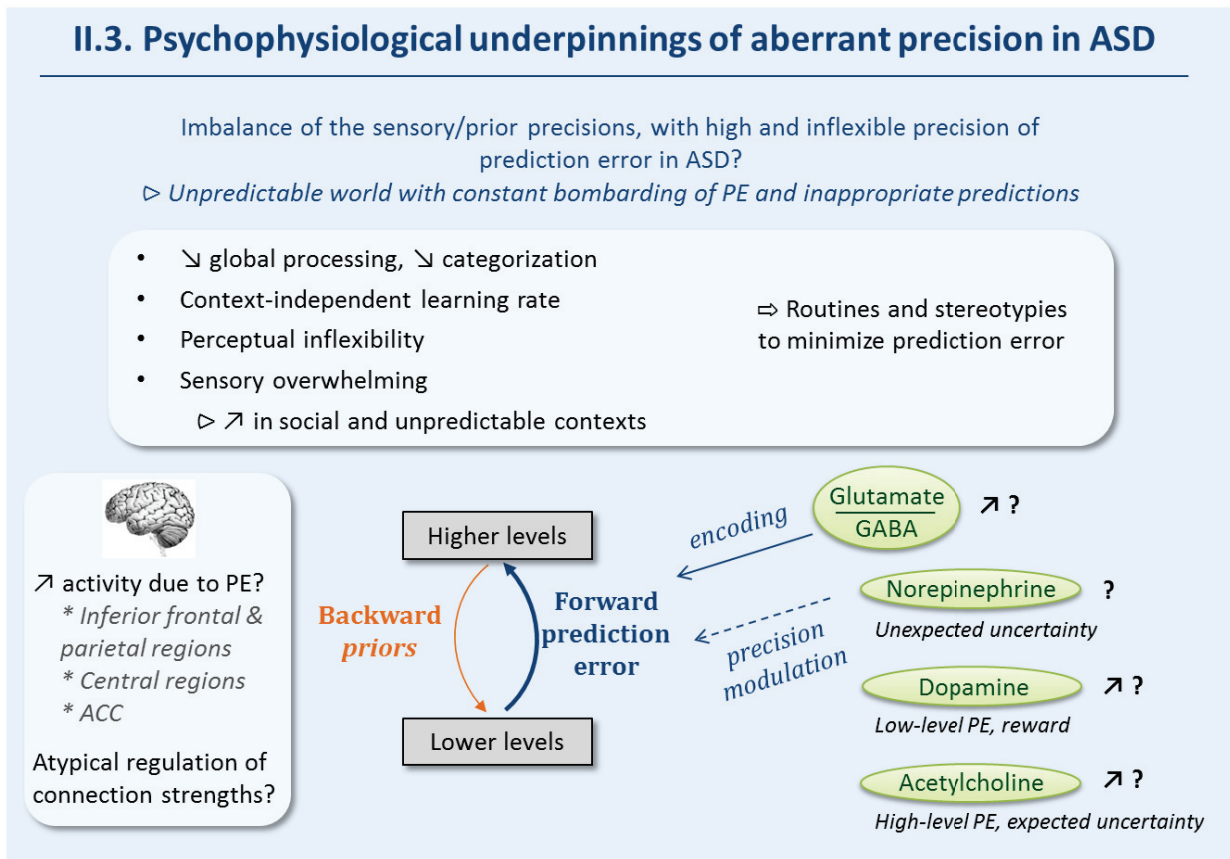
Top: Fast, slow and tonic dopaminergic functions.  
Bottom: Dopaminergic neuronal representation of the value of the prediction error (PE).

## Oxytocin

As oxytocin activity initiates synchronized neuronal activity (Rossoni et al. 2008) and interacts with the previously mentioned neurotransmitters (GABA, glutamate, acetylcholine, norepinephrine, and dopamine), Quattrocki and Friston (2014) suggested that oxytocin might contribute to PE precision control. More specifically, they propose that oxytocin might control interoceptive precision for accurate inference, then defining top-down modulations that mediate attention and sensory attenuation.

Figure 34 summarizes the behavioral, neural and molecular underpinnings of perceptual inference in ASD.

**Figure 34 : Summary of part II.3**



### III. Hypotheses and objectives

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Autism spectrum disorder is a complex and heterogeneous neurodevelopmental disorder. Despite the few theories that have been formulated over the past decades, ASD still lacks clear explanation of all of its symptoms. Recently, ASD has been viewed in the light of the Bayesian brain theory. The latter assumes that the brain is proactive, constantly generates predictions about incoming stimuli, and models its environment. Importantly, the main statistical regularities of our environment are captured by our brain, and constitute priors. Perception is then biased toward prior knowledge, with our percepts emerging from the weighted combination of sensory inputs and priors. Mismatches between priors and sensory inputs lead to the generation of prediction errors, which can be used to update priors, and so, to have a more accurate representation of the environment. Several theoretical proposals were formulated within the Bayesian framework to explain social and non-social symptoms of ASD. ASD could be characterized by an atypical imbalance of precision or weight between the predictions and the sensory inputs. The main theories suggest a relative decrease of prior precision (Pellicano and Burr 2012), a relative increase of sensory precision (Brock 2012), or a high and inflexible precision of prediction error (Van de Cruys et al. 2014).

This thesis work started where these hypotheses needed to be disentangled and required empirical evidence, so as to refine these theories. The main objective was to characterize perceptual inference and learning in ASD, within the Bayesian framework. Such a characterization required to explore prior learning and adjustment, sensory encoding, and prediction error precision modulation. In order to decrease the potential differences in prior knowledge between ASD and controls, we tested these hypotheses in a non-social context.

#### *Study I: Characterization of sensory profiles in subjects with high autism-spectrum quotient*

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To start with, we used questionnaires aiming at better characterizing hyper and hyposensitivity in ASD. To do so, we translated the Glasgow Sensory Questionnaire (Robertson and Simmons 2013) and investigated the relationships between autistic traits and sensory peculiarities. We further used these questionnaires to understand whether the atypical learning and perception studied in the following experiments were simply explained by a particular sensory sensitivity or by other deeper processes. This study was completed by the analysis of a qualitative questionnaire, established by a person with ASD. It offered the possibility to explore how predictability and context influenced sensory sensitivity.



*Study II: Characterization of the learning strategies spontaneously used in ASD*

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We then questioned whether individuals with ASD would present with atypical learning strategies, reflecting atypical encoding of sensory information and atypical prior construction. A recent theory opposed two learning strategies: the INT (*Interpolation*) learning style allowing interpolation between items to make categories, and the LUT (*Lookup table*) learning style storing each item very precisely and independently (Qian and Lipkin 2011). The authors assumed that individuals with ASD would use the INT strategy to a lower extent than NT, and would be biased toward the LUT style, which prevents from generalizing and making predictions. Previous studies investigated categorization in various contexts, and suggested decreased abilities to generalize in ASD, despite some inconsistent results. Our aim, here, was to investigate whether they would spontaneously make use of the INT or LUT learning style, when both strategies can be freely chosen. In a learning associative visual task, we hence investigated how perceptual information is processed during a cognitive task.

*Study III: Characterization of prior construction and adjustment in ASD*

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Exploring learning strategies and sensory peculiarities in cognitive tasks or situations was a first step, which was followed by the study of prior learning and sensory encoding in a series of low-level tactile tasks. These tasks aimed at determining whether participants with ASD were able to implicitly learn and contextually adjust priors in stable and variable environments, whether they would have a more precise sensory encoding than NT, and whether prior weight (and therefore prediction error weight) would be modulated by the context. To study these processes at a low-level, we made use of the so-called “time-order effect” in which the relative weight of priors and sensory encoding can be directly inferred from perceptual decisions. In order to refine these characterizations and to estimate the precision of priors, sensory inputs, and prediction errors, we developed a computational model of this task.

*Study IV: Characterization of the neural underpinnings of perceptual inference in ASD*

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Finally, we explored the neurophysiological underpinnings of perceptual inference and prior construction in such task with an fMRI study. Additionally, we used magnetic resonance spectroscopy to measure GABA and glutamate concentrations in sensory regions so as to determine whether it would be responsible for sensory encoding and whether it could modulate the relative weight of prior and sensory information on perception.



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# EXPERIMENTAL RESULTS

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## I. Study I: Atypical sensory sensitivity in ASD

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### *Preamble*

*« I have always had a very developed sensitivity, but not “uniformly”: I mean, I can be extremely sensitive to a specific texture, but I will not feel very cold temperatures, for instance. »*

*Participant with ASD (M.A.)*

*« I am hypersensitive to discreet noises, they prevent me from focusing on anything else. However, I do not mind hearing very loud noises. »*

*Participant with ASD (C.E.)*

*« My senses are always on the alert, and so, minor changes disturb me. »*

*Participant with ASD (A.D.)*

*« I am hypersensitive to sudden noises, the unexpected and sharp ones. They hurt my ears and make my heart beat faster. »*

*« My body has exaggerated reactions to physical contacts, and to clothes touching my skin. It scratches, it stings, it burns.»*

*« Senses of smell and taste are my assets: I am now part of an expert panel for wine tasting. »*

*Participant with ASD (I.S.)*

The peculiar perception of individuals with ASD is highly marked by their sensory sensitivity. As illustrated by participants M.A. and C.E., their sensitivity might seem quite paradoxical in the sense that it encompasses both hypersensitivity and hyposensitivity within the same sensory modality. Their atypical sensitivity impacts their daily-life to a high extent, as they need to avoid context with too intense and too complex sensory stimulations (Ashburner et al. 2013; Smith and Sharp 2013). Their atypical sensory sensitivity is often lived as a source of anxiety (Ashburner et al. 2013), but when it is controlled, it can be a source of pleasant sensations and can be used to develop certain skills, as participant I.S. did.

Importantly, uncertainty plays a key role in hypersensitivity (Neil et al. 2016), as seen in the testimonies of women with ASD (Appendix 2). Indeed, almost every participant spontaneously noticed that their hypersensitivity was problematic in unpredictable contexts only, as for participant I.S., or C.H. who specified *« I hate when someone touches me, except if I'm expecting it »*. In another testimony, participant V.A. explained that, when she was a child, she was hypersensitive to bath temperature, but could handle extremely hot baths if she was controlling the temperature. This testimony shows that she could be either hypersensitive

or hyposensitive, in an unexpected versus controlled situation. Participant V.A. added: « *Pain is unbearable when it is unexpected. Surprise effects are unsupportable, more than pain itself* » (Appendix 2). Similarly, Tammet explained: « *Often, the noise was more impromptu than loud. It was mostly because I did not expect it that it affected me* » (Tammet 2007). Schovanec underlined that « *the main source of anxiety for people with autism is, for sure, changes from what was expected* » (Schovanec 2013).

Previous theories of ASD hardly explained this atypical sensory sensitivity, and had troubles finding explanations for the presence of both hypersensitivity and hyposensitivity. For instance, theories which interpreted hypersensitivity as a consequence of enhanced local processing could not justify why stimulus predictability would influence sensitivity. Within the Predictive coding framework, hypersensitivity amounts to an increased weight given to sensory prediction error, and conversely, hyposensitivity is due to a decreased weighting of incoming signals. Importantly, those weightings correspond to the precision, importance or confidence attributed to this new information. They have to be also inferred from the context. Hence both hyper and hypo sensitivity may be explained by atypical, sub-optimal, adjustment of relative precisions given to incoming prediction error signals and prior expectations previously inferred or inbuilt. Such inflexibility, in particular with keeping precision high, could explain why ASD subjects would be more responsive to sensory stimuli and fine fluctuations of their sensory environment.

We asked the subjects involved in our experiments to fill out a questionnaire measuring sensory sensitivity. We were interested in assessing how a self-reported measure of sensitivity could reflect or complement behavioral and physiological measures of sensitivity and learning. We chose to use the Glasgow Sensory Questionnaire (GSQ), which is a relatively short questionnaire assessing hypersensitivity and hyposensitivity in every sensory modality (Robertson and Simmons 2013). Remarkably, the GSQ score is highly correlated with the autism spectrum quotient (AQ) (Baron-Cohen et al. 2001), and this correlation is stronger than the ones obtained with the Adult/Adolescent Sensory Profile or the Cardiff Anomalous Perceptions scale (Horder et al. 2014). As the GSQ had not been translated into French, we first translated it and validated it according to the Universalist model of cross-cultural adaptation (Herdman et al. 1998), with 245 participants. We further explored the sensory profiles of hypersensitivity and hyposensitivity in subjects with low and high AQ. This study aimed at (1) validating a French version of the GSQ, (2) better characterizing sensory sensitivity in populations with different degrees of autistic traits, and (3) providing a tool to assess sensory sensitivity in participants to the subsequent experiments of this work.

*Article*

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The Glasgow Sensory Questionnaire: validation of the French version  
and refinement of sensory profiles  
of people with high Autism-Spectrum Quotient

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*Authors:* Laurie-Anne Sapey-Triomphe, Annie Moulin, Sandrine Sonié, Christina Schmitz

*Abstract*

Sensory sensitivity peculiarities represent an important characteristic of Autism Spectrum Disorders (ASD). We first validated a French language version of the Glasgow Sensory Questionnaire (GSQ) (Robertson and Simmons 2013). The GSQ score was strongly positively correlated with the Autism-Spectrum Quotient (AQ) ( $r = .81, p < 10^{-6}, n = 245$ ). We further examined sensory profiles of groups with high versus low AQ. The high AQ group scored higher at the GSQ than the low AQ group for every sensory modality. Moreover, the high AQ group showed greater consistency in their patterns of hypersensitivity and hyposensitivity between sensory modalities, and stronger correlations between hyper and hyposensitivity. Results are discussed in the context of theories accounting for atypical sensory perception in ASD.

**Keywords:** Autism Spectrum Disorder, Autism Spectrum Quotient, Glasgow Sensory Questionnaire, hypersensitivity, cross-cultural adaptation.

## *Introduction*

Autism Spectrum Disorder (ASD) is primarily characterized by deficits in social communication and interactions, and by restricted and repetitive patterns of behaviors, interests or activities. Yet, sensory abnormalities were added as a core symptom of ASD in the last version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5, American Psychiatric Association 2013). Indeed, a new criterion emerged in the restrictive and repetitive behavior section: one of the features is now having hyper- or hypo-reactivity to sensory inputs or unusual interest in sensory aspects of the environment. Interestingly, sensory abnormalities had been already noted by Kanner and Asperger in their early descriptions of autism (Asperger 1944; Frith 1991; Kanner 1943). As ASD diagnosis is now clearly associated with atypical sensory sensitivity, it seems important to better describe and quantify peculiarities in each sensory domain.

Hyposensitivity and hypersensitivity are both present in ASD (Baranek et al. 2006; Baum et al. 2015), and are associated with under- or over-responsiveness to sensory stimuli (Green et al. 2013; Haigh et al. 2016; Tavassoli et al. 2014), as well as sensation seeking or avoidance (Ashburner et al. 2013; Baranek et al. 2006; Crane et al. 2009). Additionally, unusual sensory interests were associated with more severe autistic symptoms (Zachor and Ben-Itzhak 2013), as measured with the ADI (Le Couteur et al. 2003) and ADOS (Lord et al. 2000). Atypical sensory sensitivity has been described in every sensory modality (Baum et al. 2015; Foxe et al. 2015; Kern et al. 2007; Marco et al. 2011): in the visual (Simmons et al. 2009), auditory (Haesen et al. 2011; Sinclair et al. 2016), olfactory (Bennetto et al. 2007; Dudova et al. 2011; Wicker et al. 2016), gustatory (Bennetto et al. 2007; Tavassoli and Baron-Cohen 2012), tactile (Blakemore et al. 2006; Cascio et al. 2008; Güçlü et al. 2007; Puts et al. 2014), vestibular (Kern et al. 2007) and proprioceptive (Riquelme et al. 2016) modalities. Hyper-reactivity to sensory inputs has been one of the main findings. Between 90% and 96% of the individuals with ASD would be concerned with sensory abnormalities (Crane et al. 2009; Leekam et al. 2007; Marco et al. 2011).

The relationships between sensory sensitivity peculiarities and autistic traits have been investigated using questionnaires (Horder et al. 2014; Robertson and Simmons 2013; Takayama et al. 2014; Tavassoli, et al. 2014). The Autism-Spectrum Quotient (AQ) (Baron-Cohen et al. 2001) is a self-administered questionnaire investigating autistic traits in adults with no intellectual disability. The AQ is made of 50 items assessing social skills, attention switching, attention to details, communication and imagination. Horder and colleagues

studied the correlations between the AQ and self-reported measures of sensory sensitivity (Horder et al. 2014). Measures of sensitivity were collected with three questionnaires: the Adult/Adolescent Sensory Profile (AASP) (Brown and Dunn 2002), the Cardiff Anomalous Perceptions Scale (Bell et al. 2006) and the Glasgow Sensory Questionnaire (GSQ) (Robertson and Simmons 2013). The scores at the three questionnaires were all positively correlated with the AQ (Horder et al. 2014), with the GSQ showing the strongest correlation. Further, the AASP was not specifically developed for individuals with ASD, whereas the GSQ targets sensory experiences that can be encountered in the daily-life of people with ASD or high AQ. In addition, the AASP investigates only five sensory modalities, whereas the GSQ assesses seven sensory modalities.

The GSQ is a 42-item self-questionnaire measuring the frequency of atypical sensory processing events (Robertson and Simmons 2013). It investigates both hypersensitivity and hyposensitivity in the visual, auditory, olfactory, gustatory, tactile, vestibular and proprioceptive modalities. Strong positive correlations between the GSQ score and the AQ were found in populations including people with low and high AQ (Robertson and Simmons 2013), or including neurotypical and ASD individuals (Takayama et al. 2014; Ward et al. 2017). Previous studies on the GSQ analyzed the total GSQ score or the GSQ subscores per sensory modality, but did not detail the scores of hypersensitivity and hyposensitivity separately (Robertson and Simmons 2013; Takayama et al. 2014). Such added value would be useful to better characterize sensory profiles in groups of individuals with low and high AQ. It would help showing whether sensory peculiarities increase linearly when the AQ increases, or whether atypical sensory profiles characterize people with high AQ or ASD. The second assumption would be associated with a distinct pattern of hyper and hyposensitivity GSQ scores across modalities in a high AQ group as compared to a low AQ group, and by a non-linear relationship between the AQ and GSQ scores across the whole AQ range.

The structure of the GSQ and the fact that it was specifically developed to target the sensory issues associated with ASD make it a powerful tool to describe sensory profiles in ASD. As research on sensory sensitivity in ASD is a growing topic, it is important to have a tool that enables to individually quantify subjective sensitivity in behavioral or neuroimaging studies. In addition, it could help defining groups of participants with clearly established and/or homogeneous sensory profiles. Apart from research purposes, refining sensory sensitivity profiles could also contribute to define better sensory environments for individuals with high AQ or with ASD, by providing a somewhat comprehensive definition of their sensory sensitivity. As subjective reports show that unusual sensory experiences have a



significant impact on the daily life of individuals with ASD (Kirby et al. 2014; Robertson and Simmons 2015), a tool quantifying these experiences is necessary.

The GSQ was originally designed in English (Robertson and Simmons 2013) and its Japanese translation has been validated (Takayama et al. 2014). The GSQ needs to be cross-culturally adapted and translated to be used as a standard across international studies. The process of cross-cultural adaptation of a questionnaire involves more than a simple translation: according to the Universalist model of cross cultural adaptation of health questionnaires (Herdman et al. 1998), six types of equivalences between the original questionnaire and the translated questionnaire must be considered. Semantic equivalence relates to the translation and operational equivalence deals with the way the questionnaire can be presented, administered and scored. Item and conceptual equivalences deal with how the concepts are equivalent between one country and another, and this equivalence can be tested by comparing internal structures of the questionnaires obtained in several languages and/or countries. In order to validate the translation of a questionnaire, its internal structure should show the same main factors regardless of the country and/or language it is in. From the way the GSQ is constructed, we would expect either a structure reminding of the seven sensory modalities tested, or separating hyposensitivity from hypersensitivity items regardless of the sensory modality tested, or a mix of the two. The analysis of the internal structure would also potentially allow a distinction between populations, not only based on a global score, but also on differential relationships between the items of the questionnaire. Hence, we analyzed the GSQ internal structure on a high AQ group and of a low AQ group, using both factor analysis and hierarchical cluster analysis, the latter giving a unique picture of the dimensionality of a scale. As the GSQ was recently developed (2013), the GSQ internal structure has not been assessed yet, so we provide detailed factor analysis results to allow comparison with further cross-cultural adaptation studies of the GSQ. The last two equivalences, within the Universalist framework, comprise measurement equivalence, that deals with psychometric properties, indices of internal consistency and construct validity, and functional equivalence, that assesses the overall equivalence of results of questionnaires used in different languages/countries.

The present work had two main aims: (1) the validation of a French language version of the GSQ according to the Universalist model of cross-cultural adaptation (Herdman et al. 1998), and (2) the refinement of the sensory profiles of individuals with high or low AQ. To do so, the GSQ and AQ questionnaires were fulfilled by adults. We specifically targeted neurotypical participants and participants suspected to have ASD. Aim 1 involved the

exploration of the reliability, construct validity and internal structure of the questionnaire, and a comparison of results with the available studies using the GSQ (Horder et al. 2014; Robertson and Simmons 2013; Takayama et al. 2014; Ward et al. 2017). Aim 2 involved the analysis of sensory sensitivity profiles in groups of participants with low or high AQ. The relationships between hypersensitivity and hyposensitivity scores were compared between groups in order to know whether the high AQ group would show a specific sensory sensitivity profile, besides from higher GSQ scores. Within groups, hyper- and hypo-sensitivity scores were compared in each of the seven sensory modalities to assess whether hyper or hyposensitivity predominated. Finally, the cluster and factor analyses performed in each group enabled a clearer description of the sensory profiles and of the GSQ response consistency in each group.

## *Material and Methods*

### *Participants*

This study involved 245 participants (114 females and 131 males, mean age: 32.1 ±10.8 years old). Demographic data are described in *Table 1*. Participants anonymously completed the AQ and the GSQ, as well as a short demographical questionnaire asking for age, education level (number of years of formal education), gender, and diagnosis (“*ASD diagnosis*”, “*no ASD diagnosis*” and/or “*other psychiatric or neurologic trouble*”). One-hundred and forty-five participants reported having no diagnosis of ASD, and 95 participants reported having a formal ASD diagnosis. Inclusion criteria were being aged between 18 and 65, declaring to not suffer from other psychiatric or neurological troubles, and having filled up the three questionnaires entirely. Participants were informed that it would take about 25 minutes to complete the three questionnaires. Questionnaires were first anonymously fulfilled by individuals with ASD who used to participate in our studies. One of the participants with ASD proposed to post a link to the questionnaires on her personal webpage, a blog on Asperger syndrome mostly followed by women with ASD. Finally, participants with no ASD diagnosis were participants who used to take part in our past studies, acquaintances of the laboratory members, and individuals who might have seen the questionnaires on the previously mentioned blog on Asperger syndrome (but who reported having no formal diagnosis of ASD).

<i>Demographic data</i>				
	<b>All subjects</b>	<b>Low AQ group</b>	<b>High AQ group</b>	<i>Low vs. high AQ group</i>
<i>Number</i>	245	143	102	-
<i>Females/Males</i>	114/131	58/85	56/46	<i>ns</i>
<i>Age</i>	32.1 (±10.8)	30.7 (±11.1)	34.2 (±10.2)	*
<i>Educational level</i>	13.7 (±1.1)	14.1 (±0.9)	13.3 (±1.2)	**
<i>AQ</i>	23.0 (±13.8)	12.4 (±5.1)	38.0 (±6.0)	***
<i>GSQ Total</i>	58.7 (±28.4)	41.6 (±14.7)	82.8 (±25.4)	***
<i>Hypersensitivity</i>	32.3 (±16.9)	21.9 (±8.4)	46.9 (±14.9)	***
<i>Hyposensitivity</i>	26.4 (±12.9)	19.6 (±8.0)	35.9 (±12.4)	***

**Table 1: Demographic data and descriptive statistics for the AQ and GSQ**

Numbers corresponds to the mean (± standard deviation), in all participants, in the low AQ and high AQ groups (using a cut-off of 26). Education level corresponds to the number of year of formal education (from the first year of elementary school).

The right column corresponds to results from Student t-test comparing the two groups. \*  $p < .05$ , \*\*  $p < 10^{-3}$ , \*\*\*  $p < 10^{-6}$ . *ns*: not significant ( $p > .05$ ).

AQ: Autism-Spectrum Quotient, GSQ: Glasgow Sensory Questionnaire.

### **The Autism-Spectrum Quotient questionnaire (AQ)**

The Autism-Spectrum Quotient (AQ) is a 50-item questionnaire assessing social skills, attention switching, attention to details, communication and imagination (Baron-Cohen et al. 2001). For items such as, “*I find social situations easy*”, participants have to choose which answer best describes how the item applies to them: *definitely agree*, *slightly agree*, *slightly disagree* and *definitely disagree*. Depending on the items, the answers *definitely agree* and *slightly agree* score 1 point, and the answers *slightly disagree* and *definitely disagree* score 0 point, or vice-versa. Total scores can range from 0 to 50. The higher the AQ is, the more autistic traits are found. In our study, participants completed the validated French version of the AQ (Sonié et al. 2011).

We used a standard AQ cut-off of 26 and above for the high AQ group, and an AQ below 26 for the low AQ group (Baron-Cohen et al. 2001; Sonié et al. 2013; Tavassoli et al. 2014). Sonié and colleagues (2013) showed that a cut-off score of 26 at the French version of the AQ distinguished ASD from control participants, with a sensitivity of 89% and a specificity of 98%. In the present study, the low AQ group consisted of 143 participants, including 5 individuals who reported having a formal diagnosis of ASD. The high AQ group consisted of 102 participants, including 90 individuals who reported having a formal diagnosis of ASD. The demographical data of the two groups are described in Table 1.

### ***The Glasgow Sensory Questionnaire (GSQ)***

The GSQ is a self-administered questionnaire for adults, investigating both hypersensitivity (21 questions) and hyposensitivity (21 questions) in seven sensory modalities: vision, olfaction, taste, audition, touch, proprioception, and vestibular sensations (Robertson and Simmons 2013). In each modality, three questions assess hypersensitivity, and three others hyposensitivity. The questionnaire evaluates how frequently some sensory events are experienced by the participant (for instance, “*Do you find certain noises/pitches of sound annoying?*”). Participants answer using the scale: *never* (0 point), *rarely* (1 point), *sometimes* (2 points), *often* (3 points) or *always* (4 points). Total scores can range from 0 to 168 points.

### ***Translation of the Glasgow Sensory Questionnaire***

The GSQ was translated into French, after an agreement with the authors of the original English version (A. Robertson and D. Simmons), using the guidelines setup by the European Regulatory Issues on Quality of Life Assessment (ERIQA) group (Acquadro et al. 2008). This involved a translation/expert committee, which is now considered superior to the well-known back-translation procedure (Douglas and Craig 2007; Epstein et al. 2015) of four English/French bilinguals, with expertise in autism. Once a consensus was reached, the translation was tested using a focus group of six French native participants (3 neurotypicals and 3 with ASD), representatives of the target population, whose input prompted minor changes in the wording of item number 5.

Participants were always encouraged to query if one item seemed not clear, but no requests were made and no missing answers were obtained for any of the items.

### ***Data analysis***

#### *Scores calculation*

For each participant, we calculated the total AQ score (which can range from 0 to 50), and the five AQ subscores (which can range from 0 to 10) depicting social skills, attention to skills, attention to details, communication skills, and imagination skills. In addition, we calculated the GSQ score (which can range from 0 to 168), corresponding to the sum of the hypersensitivity and hyposensitivity scores (each ranging up to 84, and made of 21 items). We also extracted the subscores corresponding to each of the seven sensory modalities (each ranging up to 24), as well as the fourteen subscores corresponding to scores of

hypersensitivity or hyposensitivity in each of the seven sensory modalities (each ranging up to 12). We calculated three coefficients of variation: one calculated across the seven sensory modalities, one across the 14 subscales (hypersensitivity and hyposensitivity scores of the seven sensory modalities), and one across the 42 items of the GSQ.

#### *Cross sample and cross language comparisons*

The scores obtained in the present study were compared to the scores obtained by Robertson & Simmons (2013), and Ward et al. (2017) English populations, and to the scores obtained by Takayama et al. (2014) in a Japanese population. The mean scores and standard deviations obtained at each question of the GSQ from the original English version were correlated to our results using Pearson correlation test. Mean scores were compared between these two versions using one-way t-test comparing our samples to the mean obtained in the English version.

#### *Internal structure analysis*

Common factor analysis was performed on the 42 GSQ items for the entire population ( $n = 245$ ), and on the 14 GSQ subscales of the low AQ and high AQ groups, using parallel analysis for number of factors extraction and oblique (oblimin) factor rotation. Separate analysis for both low AQ and high AQ group allowed to compare the internal structure of the GSQ in both groups and to identify underperforming items. For factor extraction, both the maximum likelihood and principal axis factoring methods were used (Beavers et al. 2013), but as they yielded very similar results, only the results pertaining to the maximum likelihood method are reported. In order to determine whether factors obtained on the 14 GSQ subscales reflect the same intended structure, hierarchical cluster analyses using Revelle's ICLUST algorithm (Revelle 1978, 1979) were performed. Revelle's method has been specifically designed to visualize questionnaire scales and subscales, based on two indices: alpha and beta coefficients. Alpha coefficient (mean split-half reliability) measures internal consistency, while Beta coefficient reflects factorial homogeneity (specifically, beta is the worst split-half reliability of a scale, and hence is lower than alpha). In short, the scale structure is built starting from two-item clusters showing the highest similarity between each other, and an item is added to the initial two-item cluster only if this addition improves the internal consistency (measured by alpha) and/or the factorial homogeneity (measured by beta) of the cluster. These results are given in a hierarchical tree diagram of clusters that displays the internal sub-structure of the scale, allowing the definition of homogeneous subscales. The tree

diagram connects increasingly less similar items and/or clusters from left to right: the most similar items are combined first, and the most dissimilar items are added last. Alpha and beta coefficients are provided for each cluster, and correlation coefficients are given for each connection. Alpha above .8 and beta above .7, with differences between them lower than .1 are considered good signs of homogeneity and internal consistency (Cooksey 2006). An index of goodness of fit allows a comparison of the quality of the structures. The fit of the different models to the data was checked by the RMSR method (root mean square residuals), where a value below .05 is considered a good fit, and values between .05 and .08 a fair fit (Cooksey 2006; Fabrigar et al. 1999). This technique is considered as very complementary to the more classical approach of factor analysis and is less method dependent (Cooksey 2006). Factor, cluster and internal validity measures were performed using the “Psych” package version 1.6.9 (Revelle, 2008) within the R statistical package version 3.3.1 (June 2016).

#### *Structural validity assessment*

Correlations between the AQ and GSQ scores were performed using Pearson correlation analysis. When multiple comparisons were performed, the p-value was corrected by the number of comparisons using Bonferroni correction. Hence, for correlations involving the five subscales of the AQ scores, the significance threshold was set at  $p_{\text{corrected}} < .01$ . For correlations involving the seven subscales of the GSQ scores, the significance threshold was set at  $p_{\text{corrected}} < .007$ .

#### *Group comparisons*

Comparisons of the total AQ or GSQ scores between the low and high AQ groups were examined using Student’s t tests. The differences in subscores of the GSQ were studied using three-way mixed ANOVA with factor group (two levels, inter-subjects), sensory modality (seven levels, intra-subjects) and hyper/hyposensitivity aspects (two levels, intra-subjects). Within groups, hyper and hyposensitivity scores were compared using paired Student t-tests. Correlation matrices were compared using Steiger test (Steiger 1980) (implemented in Revelle’s Psych<sup>o</sup> package). Correlation coefficients were compared between groups using Fisher r-to-z transformation.

All statistical analyses were performed using R (<http://www.r-project.org/>, version 3.3.1.) and the threshold for statistical significance was set at  $p < .05$ , and was corrected for multiple comparisons using Bonferroni correction.

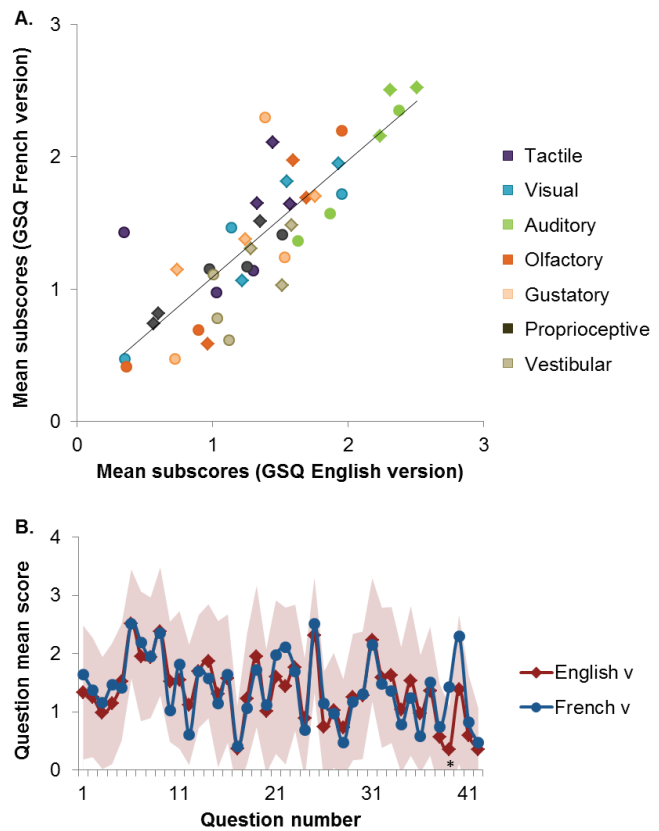
## Results

### Validation of the French version of the GSQ

#### Comparisons across samples and languages

Both the mean AQ and GSQ in the present study were very close to the ones found in the English version (Robertson and Simmons 2013): mean AQ of 23.0 ( $\pm 13.8$ ) in the French version and of 22.5 ( $\pm 10.6$ ) in the English version, mean GSQ of 58.7 ( $\pm 28.4$ ) in the French version and of 56.7 ( $\pm 23.6$ ) in the English version. The mean scores of each of the 42 questions were highly positively correlated between the English and the French versions ( $r = .83, p < 10^{-6}$ ) (Figure 1.A). Moreover, for each question, the mean score in the French version was at less than one standard deviation from the mean of the English version, except for question n°39 (French study: score =  $1.4 \pm 1.3$ , English study: score =  $0.3 \pm 0.7, t = 14, p < 10^{-6}$ ) (Figure 1.B). The standard deviations of the scores of the GSQ questions were positively correlated between the French and English versions ( $r = .63, p < 10^{-5}$ ). Finally, the correlation coefficients between the AQ and the GSQ were also very similar in the two studies (French study:  $r = .81$ ; English study:  $r = .78$ ).

The 14 GSQ subscores (hyper- or hyposensitivity scores across the seven sensory modalities) were highly correlated in our dataset and in the dataset by Ward and colleagues (Ward et al. 2017). Indeed, there was a strong correlation between the scores they got in their control group (whose mean AQ was 19) and the scores from our group of participants with



**Figure 1: Correlation between the English and the French versions of the GSQ**

A. Each sensory modality is represented by a color. Diamonds correspond to questions investigating hypersensitivity, circles correspond to questions investigating hyposensitivity.  $r = .83, p < 10^{-6}$ .

B. Scores for each question of the English version GSQ (red) and French version (blue) of the GSQ. The red shade area corresponds to the standard deviation for each item in the English version.

\* Significant difference for question n°39.

low AQ ( $r = .90, p < 10^{-4}$ ). In addition, there was a strong correlation between the scores of their ASD group and of our high AQ group ( $r = .96, p < 10^{-4}$ ).

The GSQ subscores from the seven sensory modalities obtained in our low AQ group correlated with the subscores from the control groups in the English (Ward et al. 2017) ( $r = .93, p < .01$ ) and Japanese (Takayama et al. 2014) ( $r = .82, p < .05$ ) GSQ studies.

#### *Internal reliability*

Cronbach's alpha, which assesses reliability, was equal to .95 for the all 42 items and to .94 for the 14 subscales. Per group, it was equal to .86 in the low AQ group and to .93 in the high AQ group for the 42 items. For the 14 subscales, it was equal to .84 in the low AQ group and to .91 in the high AQ group.

Item to total correlations was .59 on average, with the lowest correlation for two questions assessing olfactory hyposensitivity (question n°36 (.18) and n°17 (.33)). It was equal to .38 in the low AQ group and to .50 in the high AQ group.

#### *Factor analysis of the internal structure (42 questions, 245 subjects)*

Prior to factor analysis, ten multivariate outliers found using Mahalanobis distance with  $p < .001$  were excluded, leaving 235 cases, with a ratio of subjects per variable of 5.6.

The Kaiser-Meyer-Olkin measure of sampling adequacy (KMO) was .94 and all values for individual items were greater than .84, except for two items assessing olfactory hyposensitivity (items n°36: .58 and n°7: .78). Bartlett's test was highly significant ( $\chi^2 > 5162, p < 10^{-4}$ ), confirming that correlations between individual items were sufficient.

The maximum likelihood method was used for factor extraction. Two factors had an eigenvalue greater than 1, with percentages of variance explained of 36% and 3%. Inspection of Cattell's scree plot, parallel analysis and Velicer's MAP criterion (Velicer 1976) gave two factors. The fit of the model to the data was good, based on a RMSR result of .03, where a value below .05 is considered a good fit (Fabrigar et al. 1999; Field et al. 2012). The residuals were normal (Kolmogorov-Smirnov test = .02,  $p > .05$ ). The Tucker Lewis Index of factoring reliability was .84 and the comparative fit index (CFI) was .86, which is in the lower range of acceptable fits. The average communalities obtained across the 42 items was .39 ( $\pm .13$ ), with seven items below .30. The lowest communalities were obtained for three items investigating the hyposensitivity olfactory modality (n°7, 17 and 36).



Oblique rotation showed two underlying factors, explaining respectively 25% and 14% of variance. The correlation between these two factors was .62. The individual loadings of each factor on the 42 items are summarized here.

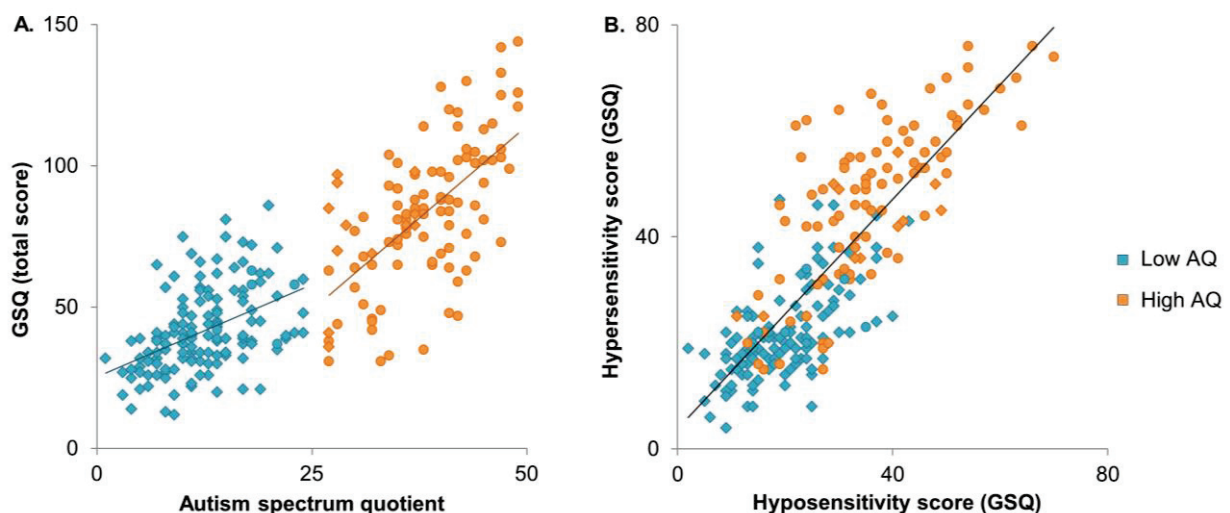
The loadings on Factor 1 involved 25 items, including 19 items assessing hypersensitivity. The highest loads (>.60) were obtained for ten hypersensitivity items.

The loadings on Factor 2 involved 16 items including 12 items with loads ranging from .41 to .71, all assessing hyposensitivity. Among these items, six showed a high degree of crossload between both factors (one gustatory, three proprioceptive and two visual). One olfactory hyposensitivity item (n°7) did not load sufficiently on any factor.

Although not every item is loading clearly on one single factor, the two-factor solution is in agreement with Factor 1 regrouping mostly hypersensitivity items and Factor 2 regrouping hyposensitivity items.

#### *Relationship between the GSQ sensory score and the AQ*

The AQ scores ranged from 1 to 49 (mean = 23.0 ±13.8), and the GSQ scores ranged from 12 to 144 (mean = 58.7 ±28.4) (Table 1). The GSQ and AQ were highly positively correlated ( $r = .81, p < 10^{-6}$ , Figure 2.A). The subscales of the AQ positively correlated with the total GSQ score. The GSQ subscales also correlated with the total AQ (Table 2). Finally, the hypersensitivity and hyposensitivity scores of the GSQ were strongly correlated ( $r = .82, p < 10^{-6}$ , Figure 2.B) in total, and for each sensory modality (Table 3).



**Figure 2: Correlations with the Glasgow Sensory Questionnaire**

A. Positive correlation between GSQ score and AQ in subjects with low (blue) or high AQ (orange). Linear regression in low AQ:  $r = .45, p < 10^{-6}$  ( $y = 1.3x + 25.5$ ), in high AQ:  $r = .62, p < 10^{-6}$  ( $y = 2.6x - 16.0$ )

B. Positive correlation between the main subscales of the GSQ: the hypersensitivity and the hyposensitivity scores in subjects with low AQ (blue) or high AQ (orange). Linear regression:  $r = .82, p < 10^{-6}$ .

Circles correspond to participants who reported having a formal diagnosis of ASD, while diamonds correspond to participants who reported having no formal diagnosis of ASD. Note that these diagnoses were not checked, and only depend on the information they volunteered.

<b>Correlations between the GSQ and AQ subscales</b>				
	<b>All subjects</b>	<b>Low AQ</b>	<b>High AQ</b>	<i>Low vs. high AQ group</i>
	<i>r</i>	<i>r</i>	<i>r</i>	
<b>Correlations with the total Glasgow Sensory Questionnaire score</b>				
AQ Social skills	.76 <sup>***</sup>	.28 <sup>**</sup>	.47 <sup>**</sup>	<i>ns</i>
AQ Attention switching	.70 <sup>***</sup>	.21 <sup>*</sup>	.38 <sup>**</sup>	<i>ns</i>
AQ Attention to detail	.66 <sup>***</sup>	.38 <sup>**</sup>	.47 <sup>***</sup>	<i>ns</i>
AQ Communication	.77 <sup>***</sup>	.28 <sup>**</sup>	.52 <sup>***</sup>	<.05
AQ Imagination	.61 <sup>***</sup>	.13	.21	<i>ns</i>
<b>Correlations with the Autism-Spectrum quotient</b>				
GSQ Hypersensitivity	.81 <sup>***</sup>	.37 <sup>**</sup>	.61 <sup>***</sup>	<.01
GSQ Hyposensitivity	.72 <sup>***</sup>	.44 <sup>***</sup>	.54 <sup>***</sup>	<i>ns</i>
GSQ Visual	.71 <sup>***</sup>	.39 <sup>**</sup>	.56 <sup>***</sup>	<i>ns</i>
GSQ Auditory	.80 <sup>***</sup>	.40 <sup>***</sup>	.51 <sup>***</sup>	<i>ns</i>
GSQ Gustatory	.58 <sup>***</sup>	.28 <sup>**</sup>	.45 <sup>**</sup>	<i>ns</i>
GSQ Olfactory	.64 <sup>***</sup>	.12	.45 <sup>**</sup>	<.01
GSQ Tactile	.71 <sup>***</sup>	.30 <sup>**</sup>	.54 <sup>***</sup>	<.05
GSQ Vestibular	.71 <sup>***</sup>	.41 <sup>***</sup>	.47 <sup>***</sup>	<i>ns</i>
GSQ Proprioceptive	.76 <sup>***</sup>	.39 <sup>**</sup>	.57 <sup>***</sup>	<i>ns</i>

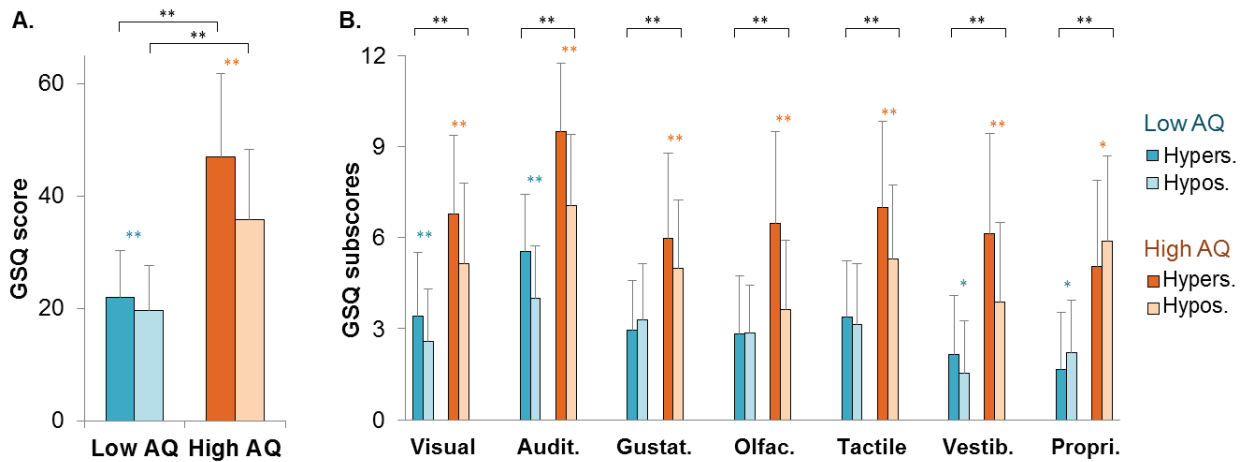
**Table 2: Correlations between the GSQ and AQ subscales**

Correlations between the GSQ and AQ subscores in all subjects, in the low AQ and in the high AQ groups. Pearson correlation tests: \*  $p < .01$ , \*\*  $p < 10^{-3}$ , \*\*\*  $p < 10^{-6}$  (non-significant for  $p > .01$  for the five AQ subscales,  $p > .025$  for the two hypersensitivity and hyposensitivity scales,  $p > .007$  for the seven sensory GSQ subscales, after Bonferroni correction).

Correlation coefficients were compared between groups using a Fisher  $r$ -to- $z$  transformation and results are shown in the right column *ns* = non-significant.

### **Group comparison: low AQ versus high AQ**

The demographic data of the two groups and basic descriptive statistics are given in Table 1. The average AQ of the low AQ group was 12.4 ( $\pm 5.1$ ), while the high AQ group scored 38.0 ( $\pm 6.0$ ) in average (group difference:  $t = 35$ ,  $p < 10^{-6}$ ). The GSQ was significantly higher in the high AQ group than in the low AQ group for the total score ( $82.8 \pm 25.4$  vs.  $41.6 \pm 14.7$ ,  $t = 15$ ,  $p < 10^{-6}$ ), the hypersensitivity score ( $46.9 \pm 14.9$  vs.  $21.9 \pm 8.4$ ,  $t = 15$ ,  $p < 10^{-6}$ ), and the hyposensitivity score ( $35.9 \pm 12.4$  vs.  $19.6 \pm 8.0$ ,  $t = 12$ ,  $p < 10^{-6}$ ) (Figure 3.A).



**Figure 3: Glasgow sensory questionnaire scores in the low AQ and high AQ groups**

A. GSQ scores of hypersensitivity and hyposensitivity in the low AQ (blue) and high AQ (orange) groups.

B. Subscales of the GSQ in the low AQ (blue) and high AQ (orange) groups, for the visual, auditory, gustatory, olfactory, tactile, vestibular and proprioceptive modalities. Black stars indicate significant difference between groups for the total GSQ subscore in each modality.

Clear blue and orange indicate the GSQ scores of hyposensitivity, while dark blue and orange indicate the GSQ scores of hypersensitivity. Blue and orange stars correspond to the significant differences between the hypersensitivity and hyposensitivity subscores within the low AQ and high AQ groups, respectively.

\*  $p < .007$ , \*\*  $p < 10^{-3}$ , \*\*\*  $p < 10^{-6}$  (Bonferroni correction for multiple comparisons involving the seven subscales of the GSQ gives a threshold of significance for  $p < .007$ ). Error bars correspond to standard deviations.

#### Correlation between the AQ and GSQ scores

The GSQ and AQ scores were positively correlated in both groups (low AQ:  $r = .45$ ,  $p < 10^{-6}$ , high AQ:  $r = .62$ ,  $p < 10^{-6}$ , Figure 2.A), with a significantly different linear relationship between the two groups. The relationship between the GSQ score and AQ writes as follows: [GSQ =  $1.3 \cdot \text{AQ} + 25.5$ ] in the low AQ group, and [GSQ =  $2.6 \cdot \text{AQ} - 16.0$ ] in the high AQ group. The 95% confidence intervals of the slopes were [0.87, 1.7] in the low AQ group, and [1.9, 3.3] in the high AQ group. The 95% confidence intervals of the intercepts were [19.7, 31.2] in the low AQ group and [-41.4, 9.3] in the high AQ group. Hence, the 95% confidence intervals of both slopes and intercepts did not overlap between groups.

The correlations between the subscales of the GSQ and of the AQ are described in Table 2. Fisher's  $z'$  transformations showed that correlation coefficients were significantly greater in the high AQ group than in the low AQ group for the correlation between the AQ and the hypersensitivity GSQ score ( $r = .61$  vs.  $r = .37$ ,  $t = 2$ ,  $p < .01$ ). Moreover, in the high AQ group, correlation coefficients were also stronger for the correlation between the AQ and the olfactory GSQ subscore ( $r = .45$  vs.  $r = .12$ ,  $t = 3$ ,  $p < .01$ ) and the tactile GSQ subscore ( $r = .30$  vs.  $r = .54$ ,  $t = 2$ ,  $p < .05$ ) than the low AQ group. A stronger correlation in the high AQ

group was also found between the total GSQ score and the communication AQ subscore ( $r = .52$  vs.  $r = .28$ ,  $t = 2$ ,  $p < .05$ ).

<i>Correlations between hypersensitivity and hyposensitivity scores</i>				
<i>GSQ subscales</i>	<i>All subjects</i>	<i>Low AQ</i>	<i>High AQ</i>	<i>Low vs. high AQ group</i>
	<i>r</i>	<i>r</i>	<i>r</i>	
<i>Total</i>	.82***	.60***	.73***	<i>ns</i> (.07)
<i>Visual</i>	.60***	.31**	.54***	.03
<i>Auditory</i>	.57***	.23***	.30*	<i>ns</i>
<i>Gustatory</i>	.36***	.23	.45**	<i>ns</i> (.06)
<i>Olfactory</i>	.25**	.09	.21	<i>ns</i>
<i>Tactile</i>	.57***	.15	.33**	<i>ns</i>
<i>Vestibular</i>	.54***	.18	.46**	<.05
<i>Proprioceptive</i>	.63***	.38**	.45**	<i>ns</i>

**Table 3: Correlations between the GSQ subscores of hyper- and hypo-sensitivity**

Pearson correlation tests: \*  $p < .007$ , \*\*  $p < 10^{-3}$ , \*\*\*  $p < 10^{-6}$  (non-significant for  $p > .007$ , after Bonferroni correction).

Correlation coefficients were compared between groups using a Fisher r-to-z transformation.

*ns* = non-significant.

### *GSQ hypersensitivity and hyposensitivity scores*

The hypersensitivity and hyposensitivity scores of the GSQ were highly positively correlated within groups (low AQ:  $r = .60$ ,  $p < 10^{-6}$ ; high AQ:  $r = .73$ ,  $p < 10^{-6}$ ; *Figure 2.B*, *Table 3*). Significantly greater correlation coefficients were found in the high AQ group as compared to the low AQ group for the correlations between the hypersensitivity and hyposensitivity scores for the visual ( $r = .54$  vs.  $r = .31$ ,  $t = 2$ ,  $p < .05$ ) and the vestibular ( $r = .46$  vs.  $r = .18$ ,  $t = 2$ ,  $p < .01$ ) modalities, and a marginally significant difference was found for the gustatory modality ( $r = .45$  vs.  $r = .23$ ,  $t = 2$ ,  $p = .06$ ).

The ANOVA investigating the effect of group (2 levels), sensory modality (7 levels) and hyper or hyposensitivity (2 levels) on scores, revealed a group effect ( $F(1,243) = 255$ ,  $p < 10^{-6}$ ), a sensory modality effect ( $F(6,1458) = 175$ ,  $p < 10^{-6}$ ), and a hyper/hyposensitivity effect ( $F(1,243) = 115$ ,  $p < 10^{-6}$ ) (*Figure 3*). There was an interaction between group and sensory modality ( $F(6,1458) = 11$ ,  $p < 10^{-6}$ ), and hyper/hyposensitivity ( $F(1,243) = 61$ ,  $p < 10^{-6}$ ). Finally, there was a triple interaction between group, sensory modality and hyper/hyposensitivity ( $F(6,1458) = 9$ ,  $p < 10^{-6}$ ). In both groups, the GSQ scores were higher for hypersensitivity than hyposensitivity: 21.9 ( $\pm 8.4$ ) versus 19.6 ( $\pm 8.0$ ) ( $t = 4$ ,  $p < 10^{-6}$ ) in the low AQ group, and 46.9 ( $\pm 14.9$ ) versus 35.9 ( $\pm 12.4$ ) ( $t = 11$ ,  $p < 10^{-6}$ ) in the high AQ group (*Figure 3.A*).

The high AQ group scored higher than the low AQ group at every subscale ( $p < 10^{-6}$  for every modality, *Figure 3.B*).

Within group, both the low AQ and high AQ groups reported significantly higher hypersensitivity than hyposensitivity for the visual, auditory and vestibular modalities (*Figure*

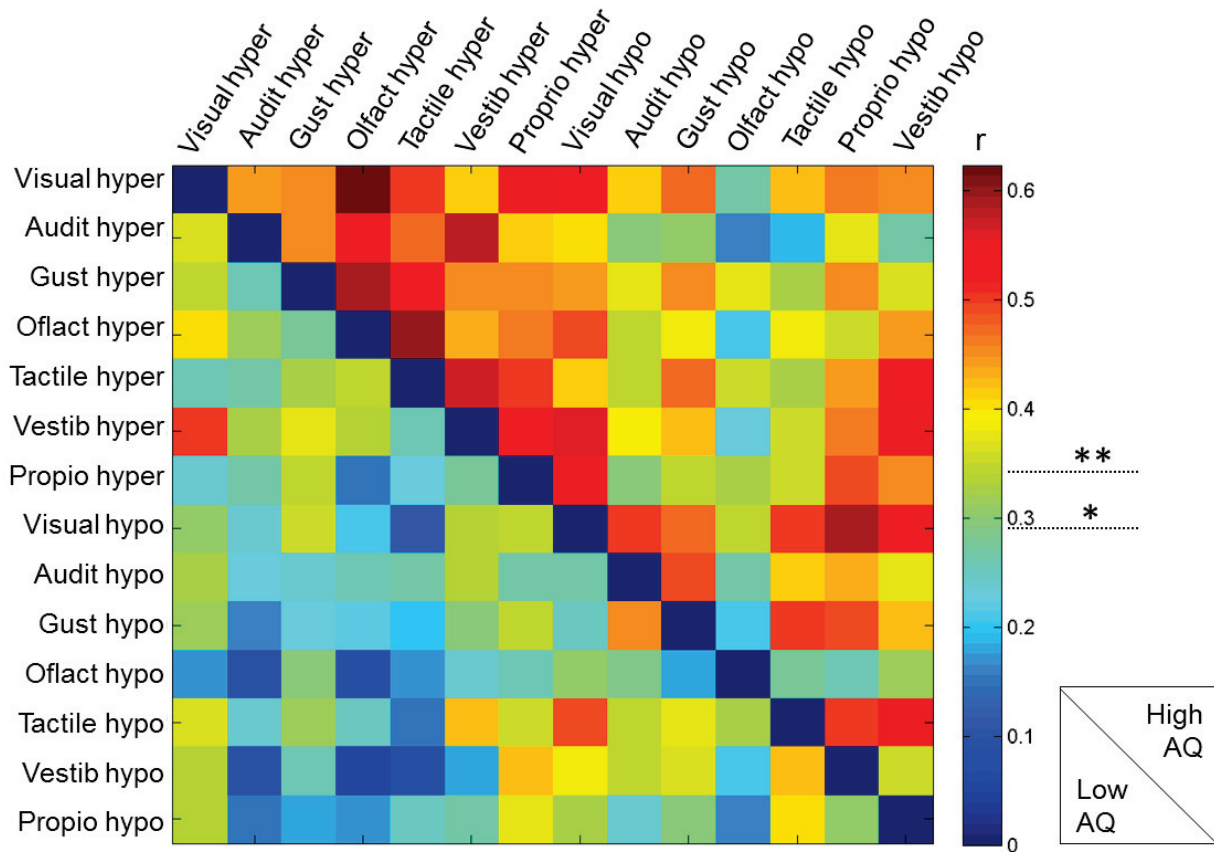
3.B). Both groups showed higher hyposensitivity than hypersensitivity for the proprioceptive modality. Contrary to the low AQ group, the high AQ group also showed significantly higher scores in hypersensitivity than hyposensitivity for the gustatory, olfactory and tactile modalities.

The difference between the hypersensitivity score and the hyposensitivity score was significantly greater in the high AQ group than in the low AQ group ( $11.0 \pm 10.2$  vs.  $2.3 \pm 7.3$ ,  $t = 6$ ,  $p < 10^{-6}$ ). In order to estimate the relative weight of the hyper and hyposensitivity scores, we divided the hypersensitivity score by the hyper plus hyposensitivity scores in each sensory modality. Results showed higher relative hypersensitivity in the high AQ group as compared to the low AQ group for the gustatory (54% vs. 47%,  $t = 3$ ,  $p < .01$ ), olfactory (64% vs. 47%,  $t = 6$ ,  $p < 10^{-6}$ ) and proprioceptive (45% vs. 35%,  $t = 3$ ,  $p < .01$ ) modalities (these  $p$ -values are all under the .007 threshold with Bonferroni correction).

#### *Correlation matrices between the GSQ subscores*

Correlation matrices between the 42 items of the GSQ showed greater correlations for the high AQ group than the low AQ group ( $\chi^2 = 1803$ ,  $p < 10^{-6}$ ), especially between items representing the same modalities. Similar differences in correlations between the 14 subscales (hyposensitivity and hypersensitivity in the seven sensory modalities) were observed, with significantly greater correlations within the high AQ group than within the low AQ group ( $\chi^2 = 220$ ,  $p < 10^{-6}$ ). Between groups, no significant differences were observed in the correlation matrices obtained with the hyposensitivity subscores ( $\chi^2 = 28$ ,  $p > .05$ ). However, highly significant group differences were obtained for hypersensitivity subscores ( $\chi^2 = 85$ ,  $p < 10^{-6}$ , *Figure 4*).

As these stronger correlations suggest greater consistency of the high AQ group responses, it led us to analyze the variation coefficient calculated for each subject across the 14 subscales. The analysis of variance showed a significantly greater variation coefficient in the low AQ group ( $64\% \pm 19$ ) than in the high AQ group ( $46\% \pm 19$ ) ( $F(1,239) = 50$ ,  $p < 10^{-6}$ ). The same differences between groups were obtained whether the variation coefficients were calculated across the seven hypersensitivity subscales, the seven hyposensitivity subscales, the 14 subscales or the 42 items ( $105\% \pm 27$  vs.  $70\% \pm 27$ ;  $F(1,239) = 101$ ,  $p < 10^{-6}$ ). This variation coefficient was negatively correlated with the GSQ score ( $r = -.78$ ,  $p < 10^{-6}$ ) and with the AQ score ( $r = -.52$ ,  $p < 10^{-6}$ ). In other words, in the high AQ group, subjects not only had greater GSQ scores but also tended to be more consistent in their answers.



**Figure 4: Correlations between the 14 GSQ subscores**

The matrix indicates the Pearson correlation coefficients between the subscores of the GSQ in the low AQ group (bottom diagonal) and in the high AQ group (upper diagonal). P-values associated with the correlation coefficients are shown with the stars on the colorbar: \*  $p < 5.10^{-4}$  (adjusted with Bonferroni correction for 91 comparisons), \*\*  $p < 5.10^{-5}$ . Audit: Auditory, Gust: Gustatory, Olfact: Olfactory, Vestib: Vestibular, Proprio: Proprioceptive, hyper: hypersensitivity, hypo: hyposensitivity.

#### *Factor analysis on the 14 subscales in the low AQ and high AQ groups*

As one of the advantages of the GSQ is to be able to test both hyposensitivity and hypersensitivity on seven sensory modalities, we proceeded with a factor analysis on the 14 subscales. This allowed to maintain a good subject to variable ratio (i.e.,  $> 7$ ) whilst being able to perform it separately on the two AQ groups: as the correlation matrices of both groups showed significant different patterns of correlations and significantly greater correlations in the high AQ than in the low AQ group, investigating a potential different internal structure between both groups seemed quite relevant.

The number of multivariate outliers excluded was 0 for the high AQ subjects and 2 for the low AQ subjects, so the factor analyses were performed on the 102 subjects with high AQ and 141 subjects with low AQ.

Skewness ranged between -.9 and .7 in the high AQ group and between .1 and 1.4 in the low AQ group. Kurtosis was below 3, except for two variables below 3.6 in the high AQ group, and six variables below 4.7 in the low AQ group. The KMO was very good (high AQ: .89, low AQ: .86), and all values for individual items were greater than .82 (olfactory hyposensitivity) in the high AQ group, and greater than .76 (auditory hypersensitivity) in the low AQ group. Bartlett's test was highly statistically significant (high AQ:  $\chi^2 > 660, p < 10^{-4}$ ; low AQ:  $\chi^2 > 524, p < 10^{-4}$ ), confirming that correlations between individual items were sufficient.

The maximum likelihood method was used for factors extraction. Inspection of Cattell's scree plot gave a number of factors of one or two in the high AQ group and of two in the low AQ group. Parallel analysis gave one factor in the high AQ group, and two factors in the low AQ group. Finally, Velicer's MAP criterion gave two factors in both groups. For both groups, only one factor had an eigenvalue greater than 1. Hence, we tested the option with either one factor or two factors.

The two factors explained 48% of variance in the high AQ group (43% and 5%) and 36% of variance in the low AQ group (30% and 6%). The model fit was good based on a RMSR result of .06 in the high AQ group and .05 in the low AQ group. The residuals were normal in both groups ( $p > .05$  in both groups). The Tucker Lewis Index of factoring reliability was .94 in the high AQ group and .97 in the low AQ group. There were very good CFI: .96 in the high AQ group and .98 in the low AQ group.

The one-factor option explained 43% of the variance in the high AQ group and 30% of variance in the low AQ group. It gave a model with lower fits indexes: Root Mean Square Error of Approximation of .09 in the high AQ group and .07 in the low AQ group, RMSR of .07 in the high AQ group and .08 in the low AQ group, Tucker Lewis  $< .90$  in both groups and CFI at .91 in both groups. Hence the two-factor extraction was selected for both groups.

The average communality obtained across the 14 variables was .48 ( $\pm .1$ ) in the high AQ group and .36 ( $\pm .09$ ) in the low AQ group. In the high AQ group, they were all above .45, except for the olfactory hyposensitivity score at .18 and the auditory hyposensitivity score at 0.38. In the low AQ group, all communalities were between .21 and .51.

Oblique rotation showed two underlying factors, explaining respectively 25% and 24% of variance in the high AQ group, and 20% and 16% of variance in the low AQ group. The correlation between the two factors was .66 in the high AQ group and 0.53 in the low AQ group. The individual loadings of each factor on each of the 14 variables are summarized below.

*High AQ group*

In the high AQ group, the seven hypersensitivity scores loaded on Factor 1, with some degrees of cross-loadings for the proprioceptive, visual and vestibular modalities. The seven hyposensitivity scores loaded on Factor 2, with a low load for the olfactory hyposensitivity score and the highest load for the tactile hyposensitivity score (.84).

Hierarchical cluster analysis revealed a homogeneous main cluster (C12, with  $\alpha = .91$ ,  $\beta = .84$ ) and two main subclusters: one associated with hypersensitivity variables (C11, with  $\alpha = .88$ ,  $\beta = .82$ ) and one associated with hyposensitivity variables (except for the olfactory hyposensitivity variable) (C9,  $\alpha = .85$ ,  $\beta = .80$ ) (Figure 5). However, the addition of the olfactory hyposensitivity variable led to a drop in homogeneity ( $\beta = .6$ ), showing that this variable did not fit well. Likewise, when we force the number of final clusters to be 2, the olfactory hyposensitivity variable was excluded as a single item cluster, while the rest of the structure was identical to the previous main cluster (C12) with two hyposensitivity and hypersensitivity subclusters. For the entire structure (excluding the olfactory hyposensitivity variable), the minimum  $\alpha$  and  $\beta$  were .66 and above .80 for the main subclusters, with a difference between them lower than .08. This result argues for the unidimensionality of the structure, with two subclusters corresponding to hyposensitivity and hypersensitivity.

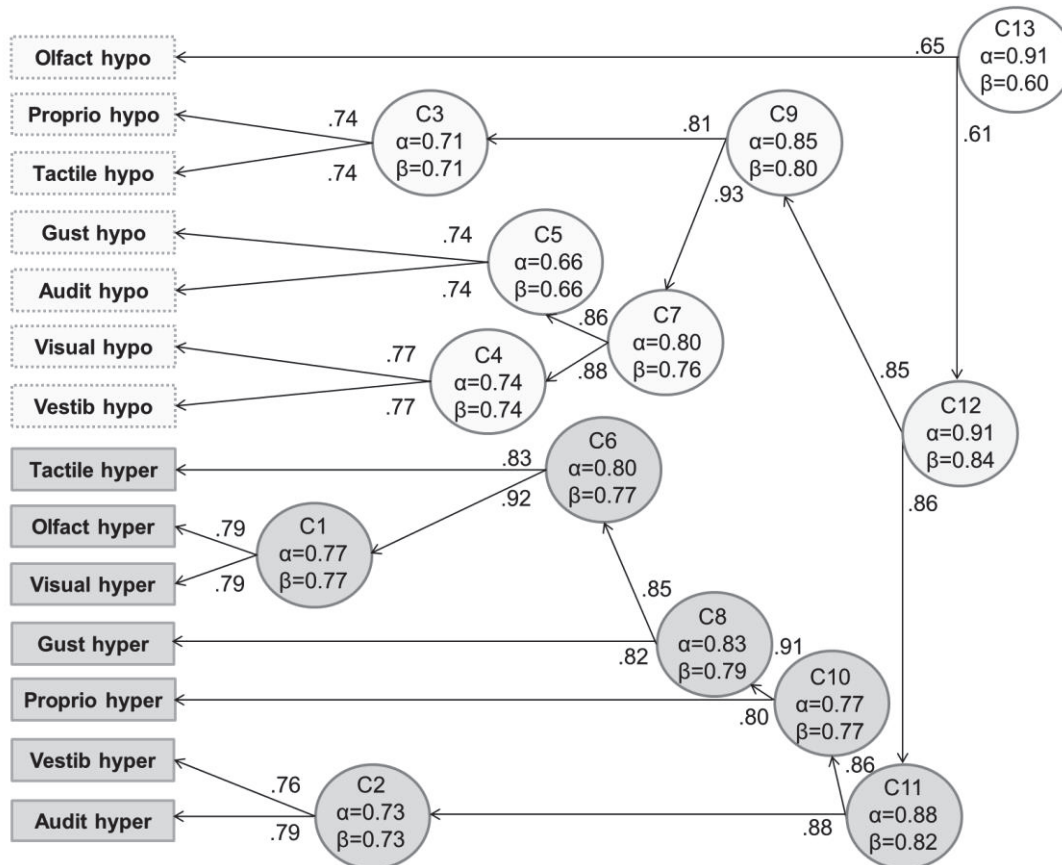


Figure 5: Hierarchical cluster analysis of the 14 GSQ subscales in the high AQ group



*This analysis revealed the cluster C11 associated with the hypersensitivity subscores, the cluster C9 associated with the hyposensitivity subscores. The main cluster C12 gathers the hypersensitivity and hyposensitivity clusters. The addition of the olfactory hyposensitivity item in cluster C13 led to a drop in homogeneity ( $\beta=0.6$ ) suggesting a poor fit of this item.*

*Hyper: hypersensitivity, Hypo: hyposensitivity score at the GSQ*

### *Low AQ group*

In the low AQ group, the seven hyposensitivity variables and the proprioceptive hypersensitivity variable loaded on Factor 1. The six remaining hypersensitivity variables loaded on Factor 2. There was some cross-loading with the gustatory hypersensitivity and auditory hyposensitivity variables, and to a lesser degree, with the visual hypersensitivity variable.

Cluster analysis performed on the low AQ group revealed a somewhat foggier pattern than for the high AQ group, with lower  $\alpha$  and  $\beta$  coefficients (mostly ranging between .6 and .7) and more heterogeneity. A main cluster was clearly identified (C11, with  $\alpha = .84$ ,  $\beta = .74$ ), regrouping two main subclusters, corresponding to hyposensitivity (C10, with  $\alpha = .80$ ,  $\beta = .71$ ) and hypersensitivity (C8, with  $\alpha = .72$ ,  $\beta = .69$ ). The proprioceptive hypersensitivity variable was associated with the vestibular hyposensitivity variable, and was part of the hyposensitivity cluster, as in the factor analysis. The addition of the olfactory hyposensitivity and auditory hypersensitivity variables yielded a drop in beta coefficient (i.e. a loss of homogeneity), suggesting that those two items did not fit well and had a somewhat different behaviour than the rest of the scale.

## *Discussion*

This study aimed at validating a French language version of the Glasgow Sensory Questionnaire and at refining the characterization of sensory sensitivity profiles in individuals with low and high AQ. Our results validate the French-language version of the GSQ, within the framework of the equivalences defined by the Universalist Model of cross-cultural adaptation of health questionnaires (Herdman et al. 1998). Overall, this study confirms the strong relationship between the number of autistic traits and the frequency of unusual sensory experiences. We also defined precise sensory profiles of hypersensitivity and hyposensitivity across sensory modalities in individuals with low and high AQ, and we characterized group differences.

### ***Validation of the French version of the GSQ***

The strong correlations obtained across the 42 items between the French and English (Robertson and Simmons 2013) studies are in favor of good item equivalence between languages. Item equivalence between population samples was also respected as scores at the fourteen subscales of the present study and of the study by Ward and colleagues (2017) strongly correlated. The French GSQ showed a very good internal consistency, in line with the ones reported in the English and Japanese versions of the GSQ (Robertson and Simmons 2013; Takayama et al. 2014). Functional equivalence, dealing with the relationships between the questionnaire and external factors, was also respected as correlations between GSQ and AQ subscales were very similar across languages and samples (Robertson and Simmons 2013; Takayama et al. 2014).

The internal structure of the GSQ had not been investigated in previous studies, but was characterized in the present study in order to determine whether it reflected the expected structure of the questionnaire. Precisely, we expected the factor analysis to reveal seven factors corresponding to the seven sensory modalities, and/or two factors corresponding to hyposensitivity and hypersensitivity, or a mix of the two. Common factor analysis performed on the entire population, yielded a two-factor structure with one factor encompassing mostly hypersensitivity items, and the other involving mostly hyposensitivity items. Hierarchical cluster analysis confirmed this structure in both AQ groups, showing a unique dimension scale (“sensory abnormality”), with two main subcomponents: hyper and hyposensitivity. However, finer grain analysis reveals differences between low and high AQ groups.

### ***Refining sensory profiles in groups with low versus high AQ***

GSQ scores increased twice more with the AQ for the high AQ group than for the low AQ group. The non-linear relationship between AQ and GSQ scores across the entire AQ range highlighted the fact that groups with low and high AQ had distinct sensory profiles. Indeed, it suggests that individuals with high AQ are not simply characterized by an increased occurrence of atypical sensory experiences, but possibly also by different sensory profiles.

Sensory profiles in groups with low and high AQ were first analyzed using cluster and factor analyses on the fourteen GSQ subscales. Factor analysis showed a similar two-factor structure (hypersensitivity and hyposensitivity) in each group, but with more variance being explained for the high AQ than for the low AQ group. Cluster analysis showed a similar structure at a macro scale, i.e., an abnormal sensitivity factor with two subcomponents,

hypersensitivity and hyposensitivity with a clearer pattern in the high AQ group, and a foggier pattern in the low AQ group. Finer grain analysis shows a slightly different relationship between the items, with a stronger homogeneity of the two subcomponents in the high AQ group versus the low AQ group. The hypo-olfactory item is clearly a “rogue” item for both groups (which is in agreement with the behavior of the corresponding items in the 42 items scale). However, cluster analysis allows to pin-point differences in how the “hyper-auditory” item behaves: it is associated with the hyper-vestibular item in the high AQ group, but behaves as an outsider for the low AQ group. In future development of sensory analysis, the differential perception of such items between the low AQ group and the high AQ group could be worth investigating. In addition, the analysis of the GSQ structure also demonstrated a greater consistency between items in the high AQ group.

The difference between groups is further illustrated by the correlations between the hypersensitivity and hyposensitivity scores in the seven sensory modalities. Indeed, the correlation matrices showed stronger correlations in the high AQ than in the low AQ group, especially for the hypersensitivity subscales. This indicates that individuals with high AQ have an “extreme” sensitivity, shared quite uniformly across the seven sensory modalities. In contrast, it suggests that individuals with low AQ would have “peaks” of increased/decreased sensitivity in a particular sensory modality, but this would not be generalized to every sensory modality. Together with the clear and robust patterns revealed by the cluster and common factor analyses, these elements show that the high AQ group had a more homogeneous profile of sensory sensitivity than the low AQ group. Interestingly, the high AQ group also showed stronger correlations between hyposensitivity and hypersensitivity scores, especially in the visual modality. It means that, contrary to people with low AQ, individuals with high AQ have a higher tendency to experience both hypersensitivity and hyposensitivity within a sensory modality.

The high AQ group scored above the low AQ group for each of the fourteen subscales, except for the olfactory hyposensitivity subscale. There was no difference either on this subscale in the comparison between control and ASD individuals in the study by Ward and colleagues (Ward et al. 2017). In our study, the two groups were also distinguished by the fact that the high AQ group reported more experiences due to hypersensitivity than hyposensitivity, as compared to the low AQ group. The relative predominance of hypersensitivity over hyposensitivity was more pronounced in the high AQ than low AQ group for the olfactory modality, and to a lower extent, for the gustatory and proprioceptive

modalities. Noticeably, enhanced olfactory hypersensitivity had been previously linked to more autistic traits (Ashwin et al. 2014).

### ***Linking sensory profiles of people with high AQ to current theories of ASD***

Theories accounting for an abnormal sensory sensitivity in ASD mostly focus on sensory hypersensitivity, and often fail to explain both hypersensitivity and hyposensitivity. The Enhanced Perceptual Functioning (EPF) theory of ASD suggested increased perceptual ability in ASD (Mottron et al. 2006; Mottron and Burack 2001). In this view, sensory hypersensitivity could contribute to superior discrimination performance or peaks of ability found in ASD. Besides, the Intense World Syndrome theory suggested that sensory hypersensitivity could be related to excessive neural processing and neural hyper-reactivity (Markram et al. 2007; Markram and Markram 2010). Furthermore, theories suggesting either an increased or decreased level of endogenous neural noise in ASD could lead to hypo- or hyper-sensitivity (Dakin and Frith 2005; Davis and Plaisted-Grant 2015; Simmons and Milne 2015; Simmons et al. 2007). Bayesian theories propose that peculiar sensory sensitivity in ASD could be due to an atypical weighting between the confidence given to the sensation relatively to the expectation on this sensation, in a specific context (Brock 2012; Haker et al. 2016; Lawson et al. 2014; Palmer et al. 2017; Pellicano and Burr 2012; Van de Cruys et al. 2013, 2014, 2016).

Our results showed quite homogeneous profiles of sensory sensitivity in the high AQ group, and sensory profiles characterized by peaks of hypersensitivity or hyposensitivity in different sensory modalities in the low AQ group. Yet, given the notion of sensory expertise in ASD, we could have expected sensory profiles with peaks of hypersensitivity more pronounced in the high AQ group than in the low AQ group. The stronger predominance of experiences of hypersensitivity over hyposensitivity in the high AQ group could contribute to explain why theories of ASD were often focused on hypersensitivity. The EPF theory (Mottron et al. 2006; Mottron, and Burack 2001) or the low endogenous noise theory of ASD (Davis and Plaisted-Grant 2015) would be consistent with the frequent hypersensitivity experiences in ASD. To explain the co-occurrence of both hyposensitivity and hypersensitivity within a sensory modality in ASD, the global context needs to be taken into account. For instance, the predictable nature of the sensory stimulations seems to play a key role in the reactivity to sensory stimuli in people with ASD (Ashburner et al. 2013). Indeed, a study based on questionnaires revealed that around half of the variance of sensory sensitivity abnormalities in ASD could be explained by anxiety and intolerance to uncertainty (Neil et al.

2016). This need for predictive stimuli fits the Bayesian brain theories suggesting that ASD individuals would have suboptimal predictive systems, particularly in changing environments (Haker et al. 2016; Lawson et al. 2014; Palmer et al. 2017; Robic et al. 2014; Van de Cruys et al. 2014, 2016). Bayesian theories could explain the presence of both hypersensitivity and hyposensitivity, as sensory reactivity would depend on the context (and particularly, of its predictability). The context should help disentangling sensory relevant information from irrelevant noise, and therefore adapt the level of precision of the sensory input (Van de Cruys et al. 2016). Hence, depending on the context, noisy sensory inputs would lead to hyposensitivity, while precise sensory inputs would lead to hypersensitivity.

### ***Implications for individuals with ASD***

As abnormal sensory sensitivity can affect the quality of life, a finer characterization of the sensory sensitivity profiles could help defining better working and living environments for individuals with high AQ or diagnosed with ASD. Based on ASD reports, Smith and Sharp (2013) suggested that heightened senses in ASD would lead to fascination and pleasurable activities, but would also trigger stress, avoidance and isolation. Atypical sensitivity can affect non-social, but also social perception. For instance, Lundqvist (2015) showed that hyper-responsiveness to touch mediated social dysfunction in ASD. For people with ASD, the major negative outcomes of hypersensitivity appear to be over-responsivity and anxiety. Indeed, sensory over-responsivity positively correlates with the AQ (Tavassoli et al. 2014) and can lead to anxiety (Ashburner et al. 2013). Anxiety disorders are more common in individuals with ASD than controls, and are closely related to sensory over-responsivity (Green and Ben-Sasson 2010). Moreover, in children with ASD, sensory over-responsivity would emerge earlier than anxiety (Green et al. 2011), and this atypical sensitivity leads to higher physiological stress (Corbett et al. 2016). Interestingly, Horder et al. (2014) showed that the correlation between the GSQ and the AQ survived correction for anxiety trait scores. To cope with atypical sensory experiences, people with ASD would use several strategies such as avoidance, meta-cognitive adaptation, or increasing the predictability of the environment (Ashburner et al. 2013).

### ***Perspectives***

With the GSQ internal structure analysis, the present work suggests that new GSQ indices could be relevant for exploring the peculiarities of perceptual processing in ASD. Replicating this study on a different high AQ population would allow ascertaining the

robustness of the associations between different sensory modalities observed here. Indeed, the robustness of those similarities should be assessed in other samples so as to determine whether these similarities are specific to ASD. Indeed, heightened hypersensitivity and hyposensitivity was also found in synaesthetes (Ward et al. 2017), and comparing the GSQ internal structure of the responses of synaesthetes and of subjects with ASD could indicate whether they show different sensory modalities associations.

Finally, future works should investigate the relationships between the GSQ scores and behavioral measures (such as perceptual thresholds) or neurophysiological data in order to estimate whether the self-report of the GSQ fits physiological data. The GSQ is designed to assess sensory sensibility in individuals with ASD who are able to complete a self-report questionnaire, hence limiting its scope to only part of the spectrum. Future works could also adapt this self-report questionnaire to an observation measurement tool for a larger use.

In conclusion, this study confirms the robust link between autistic traits and atypical sensory sensitivity. Although the GSQ is relatively recent, the similarities of behavior observed between a French sample and several other samples, with good conceptual, measurement and functional equivalences, are extremely encouraging to go toward an international standard use of the GSQ in clinical and research contexts.

## **References**

- Acquadro, C., Conway, K., Hareendran, A., Aaronson, N., & European Regulatory Issues and Quality of Life Assessment (ERIQA) Group. (2008). Literature review of methods to translate health-related quality of life questionnaires for use in multinational clinical trials. *Value in Health: The Journal of the International Society for Pharmacoeconomics and Outcomes Research*, 11(3), 509–521. doi:10.1111/j.1524-4733.2007.00292.x
- American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders*. American Psychiatric Association. <http://dsm.psychiatryonline.org/doi/book/10.1176/appi.books.9780890425596>.
- Ashburner, J., Bennett, L., Rodger, S., & Ziviani, J. (2013). Understanding the sensory experiences of young people with autism spectrum disorder: a preliminary investigation. *Australian Occupational Therapy Journal*, 60(3), 171–180. doi:10.1111/1440-1630.12025
- Ashwin, C., Chapman, E., Howells, J., Rhydderch, D., Walker, I., & Baron-Cohen, S. (2014). Enhanced olfactory sensitivity in autism spectrum conditions. *Molecular Autism*, 5(1), 53. doi:10.1186/2040-2392-5-53
- Asperger, Hans. (1944). Die ‘Autistischen Psychopathen’ im Kindesalter. *Archiv für Psychiatrie und Nervenkrankheit*, 117, 76–136.
- Baranek, G. T., David, F. J., Poe, M. D., Stone, W. L., & Watson, L. R. (2006). Sensory Experiences Questionnaire: discriminating sensory features in young children with autism, developmental delays, and

- typical development. *Journal of Child Psychology and Psychiatry*, 47(6), 591–601. doi:10.1111/j.1469-7610.2005.01546.x
- Baron-Cohen, S., Wheelwright, S., Skinner, R., Martin, J., & Clubley, E. (2001). The autism-spectrum quotient (AQ): evidence from Asperger syndrome/high-functioning autism, males and females, scientists and mathematicians. *Journal of Autism and Developmental Disorders*, 31(1), 5–17.
- Baum, S. H., Stevenson, R. A., & Wallace, M. T. (2015). Behavioral, perceptual, and neural alterations in sensory and multisensory function in autism spectrum disorder. *Progress in Neurobiology*, 134, 140–160. doi:10.1016/j.pneurobio.2015.09.007
- Beavers, A. S., Lounsbury, J. W., Richards, J. K., Huck, S. W., Skolits, G. J., & Esquivel, S. L. (2013). Practical Considerations for Using Exploratory Factor Analysis in Educational Research. *Practical Assessment, Research & Evaluation*, 18(6). Accessed 23 September 2017
- Bell, V., Halligan, P. W., & Ellis, H. D. (2006). The Cardiff Anomalous Perceptions Scale (CAPS): a new validated measure of anomalous perceptual experience. *Schizophrenia Bulletin*, 32(2), 366–377. doi:10.1093/schbul/sbj014
- Bennetto, L., Kuschner, E. S., & Hyman, S. L. (2007). Olfaction and taste processing in autism. *Biological Psychiatry*, 62(9), 1015–1021. doi:10.1016/j.biopsych.2007.04.019
- Blakemore, S.-J., Tavassoli, T., Calò, S., Thomas, R. M., Catmur, C., Frith, U., & Haggard, P. (2006). Tactile sensitivity in Asperger syndrome. *Brain and cognition*, 61(1), 5–13. doi:10.1016/j.bandc.2005.12.013
- Brock, J. (2012). Alternative Bayesian accounts of autistic perception: comment on Pellicano and Burr. *Trends in Cognitive Sciences*, 16(12), 573–574. doi:10.1016/j.tics.2012.10.005
- Brown, C., & Dunn, W. (2002). *Adult/adolescent sensory profile: user's manual*.
- Cascio, C., McGlone, F., Folger, S., Tannan, V., Baranek, G., Pelphrey, K. A., & Essick, G. (2008). Tactile Perception in Adults with Autism: a Multidimensional Psychophysical Study. *Journal of autism and developmental disorders*, 38(1), 127–137. doi:10.1007/s10803-007-0370-8
- Cooksey, R. W. (2006). Coefficient Beta and Hierarchical Item Clustering: An Analytical Procedure for Establishing and Displaying the Dimensionality and Homogeneity of Summated Scales. *Organizational Research Methods*, 9(1), 78–98. doi:10.1177/1094428105283939
- Corbett, B. A., Muscatello, R. A., & Blain, S. D. (2016). Impact of Sensory Sensitivity on Physiological Stress Response and Novel Peer Interaction in Children with and without Autism Spectrum Disorder. *Frontiers in Neuroscience*, 10, 278. doi:10.3389/fnins.2016.00278
- Crane, L., Goddard, L., & Pring, L. (2009). Sensory processing in adults with autism spectrum disorders. *Autism*, 13(3), 215–228. doi:10.1177/1362361309103794
- Dakin, S., & Frith, U. (2005). Vagaries of visual perception in autism. *Neuron*, 48(3), 497–507. doi:10.1016/j.neuron.2005.10.018
- Davis, G., & Plaisted-Grant, K. (2015). Low endogenous neural noise in autism. *Autism: The International Journal of Research and Practice*, 19(3), 351–362. doi:10.1177/1362361314552198
- Douglas, S. P., & Craig, C. S. (2007). Collaborative and Iterative Translation: An Alternative Approach to Back Translation. *Journal of International Marketing*, 15(1), 30–43. doi:10.1509/jimk.15.1.030
- Dudova, I., Vodicka, J., Havlovicova, M., Sedlacek, Z., Urbanek, T., & Hrdlicka, M. (2011). Odor detection threshold, but not odor identification, is impaired in children with autism. *European Child & Adolescent Psychiatry*, 20(7), 333–340. doi:10.1007/s00787-011-0177-1
- Epstein, J., Osborne, R. H., Elsworth, G. R., Beaton, D. E., & Guillemin, F. (2015). Cross-cultural adaptation of the Health Education Impact Questionnaire: experimental study showed expert committee, not back-translation, added value. *Journal of Clinical Epidemiology*, 68(4), 360–369. doi:10.1016/j.jclinepi.2013.07.013
- Fabrigar, L. R., Wegener, D. T., MacCallum, R. C., & Strahan, E. J. (1999). Evaluating the use of exploratory factor analysis in psychological research. *Psychological Methods*, 4(3), 272–299. doi:10.1037/1082-989X.4.3.272
- Field, Andy, Miles, Jeremy, & Field, Zoë. (2012). *Discovering Statistics Using R* (SAGE Publications Ltd.).
- Foxe, J. J., Molholm, S., Del Bene, V. A., Frey, H.-P., Russo, N. N., Blanco, D., et al. (2015). Severe multisensory speech integration deficits in high-functioning school-aged children with Autism Spectrum Disorder (ASD) and their resolution during early adolescence. *Cerebral Cortex* (New York, N.Y.: 1991), 25(2), 298–312. doi:10.1093/cercor/bht213

- Frith, U. (1991). *Autism and Asperger Syndrome*. Cambridge University Press.
- Green, S. A., & Ben-Sasson, A. (2010). Anxiety disorders and sensory over-responsivity in children with autism spectrum disorders: is there a causal relationship? *Journal of Autism and Developmental Disorders*, 40(12), 1495–1504. doi:10.1007/s10803-010-1007-x
- Green, S. A., Ben-Sasson, A., Soto, T. W., & Carter, A. S. (2011). Anxiety and Sensory Over-Responsivity in Toddlers with Autism Spectrum Disorders: Bidirectional Effects Across Time. *Journal of Autism and Developmental Disorders*, 42(6), 1112–1119. doi:10.1007/s10803-011-1361-3
- Green, S. A., Rudie, J. D., Colich, N. L., Wood, J. J., Shirinyan, D., Hernandez, L., et al. (2013). Over-Reactive Brain Responses to Sensory Stimuli in Youth With Autism Spectrum Disorders RH: fMRI Response to Sensory Stimuli in ASD. *Journal of the American Academy of Child and Adolescent Psychiatry*, 52(11). doi:10.1016/j.jaac.2013.08.004
- Güçlü, B., Tanidir, C., Mukaddes, N. M., & Unal, F. (2007). Tactile sensitivity of normal and autistic children. *Somatosensory & Motor Research*, 24(1–2), 21–33. doi:10.1080/08990220601179418
- Haesen, B., Boets, B., & Wagemans, J. (2011). A review of behavioural and electrophysiological studies on auditory processing and speech perception in autism spectrum disorders. *Research in Autism Spectrum Disorders*, 5(2), 701–714. doi:10.1016/j.rasd.2010.11.006
- Haigh, S. M., Gupta, A., Barb, S. M., Glass, S. A. F., Minshew, N. J., Dinstein, I., et al. (2016). Differential sensory fMRI signatures in autism and schizophrenia: Analysis of amplitude and trial-to-trial variability. *Schizophrenia Research*. doi:10.1016/j.schres.2016.03.036
- Haker, H., Schneebeli, M., & Stephan, K. E. (2016). Can Bayesian Theories of Autism Spectrum Disorder Help Improve Clinical Practice? *Frontiers in Psychiatry*, 7. doi:10.3389/fpsy.2016.00107
- Herdman, M., Fox-Rushby, J., & Badia, X. (1998). A model of equivalence in the cultural adaptation of HRQoL instruments: the universalist approach. *Quality of Life Research: An International Journal of Quality of Life Aspects of Treatment, Care and Rehabilitation*, 7(4), 323–335.
- Holder, J., Wilson, C. E., Mendez, M. A., & Murphy, D. G. (2014). Autistic traits and abnormal sensory experiences in adults. *Journal of Autism and Developmental Disorders*, 44(6), 1461–1469. doi:10.1007/s10803-013-2012-7
- Kanner, Leo. (1943). Autistic disturbances of affective contact., *Nervous Child*, 2, 3, 217–250.
- Kern, J. K., Garver, C. R., Grannemann, B. D., Trivedi, M. H., Carmody, T., Andrews, A. A., & Mehta, J. A. (2007). Response to vestibular sensory events in autism. *Research in Autism Spectrum Disorders*, 1(1), 67–74. doi:10.1016/j.rasd.2006.07.006
- Kern, J. K., Trivedi, M. H., Grannemann, B. D., Garver, C. R., Johnson, D. G., Andrews, A. A., et al. (2007). Sensory correlations in. *Autism*, 11(2), 123–134. doi:10.1177/1362361307075702
- Kirby, A. V., Dickie, V. A., & Baranek, G. T. (2014). Sensory experiences of children with autism spectrum disorder: In their own words. *Autism*, 1362361314520756. doi:10.1177/1362361314520756
- Lawson, R. P., Rees, G., & Friston, K. J. (2014). An aberrant precision account of autism. *Frontiers in Human Neuroscience*, 8, 302. doi:10.3389/fnhum.2014.00302
- Le Couteur, A., Lord, C., & Rutter, M. (2003). *The autism diagnostic interview-revised (ADI-R)* (Los Angeles: Western Psychological Services.).
- Leekam, S. R., Nieto, C., Libby, S. J., Wing, L., & Gould, J. (2007). Describing the sensory abnormalities of children and adults with autism. *Journal of Autism and Developmental Disorders*, 37(5), 894–910. doi:10.1007/s10803-006-0218-7
- Lord, C., Risi, S., Lambrecht, L., Cook, E. H., Leventhal, B. L., DiLavore, P. C., et al. (2000). The autism diagnostic observation schedule-generic: a standard measure of social and communication deficits associated with the spectrum of autism. *Journal of Autism and Developmental Disorders*, 30(3), 205–223.
- Lundqvist, L.-O. (2015). Hyper-responsiveness to touch mediates social dysfunction in adults with autism spectrum disorders. *Research in Autism Spectrum Disorders*, 9, 13–20. doi:10.1016/j.rasd.2014.09.012
- Marco, E. J., Hinkley, L. B. N., Hill, S. S., & Nagarajan, S. S. (2011). Sensory Processing in Autism: A Review of Neurophysiologic Findings: *Pediatric Research*, 69(5 Part 2), 48R–54R. doi:10.1203/PDR.0b013e3182130c54
- Markram, H., Rinaldi, T., & Markram, K. (2007). The intense world syndrome--an alternative hypothesis for autism. *Frontiers in Neuroscience*, 1(1), 77–96. doi:10.3389/neuro.01.1.1.006.2007



- Markram, K., & Markram, H. (2010). The Intense World Theory – A Unifying Theory of the Neurobiology of Autism. *Frontiers in Human Neuroscience*, 4. doi:10.3389/fnhum.2010.00224
- Mottron, L., & Burack, J. (2001). Enhanced perceptual functioning in the development of autism. In *The development of autism: Perspectives from theory and research* (Burack, Charman, Yirmiya, Zelazo., pp. 131–148).
- Mottron, L., Dawson, M., Soulières, I., Hubert, B., & Burack, J. (2006). Enhanced perceptual functioning in autism: an update, and eight principles of autistic perception. *Journal of autism and developmental disorders*, 36(1), 27–43. doi:10.1007/s10803-005-0040-7
- Neil, L., Olsson, N. C., & Pellicano, E. (2016). The Relationship Between Intolerance of Uncertainty, Sensory Sensitivities, and Anxiety in Autistic and Typically Developing Children. *Journal of Autism and Developmental Disorders*, 46(6), 1962–1973. doi:10.1007/s10803-016-2721-9
- Palmer, C. J., Lawson, R. P., & Hohwy, J. (2017). Bayesian Approaches to Autism: Towards Volatility, Action, and Behavior. *Psychological Bulletin*. doi:10.1037/bul0000097
- Pellicano, E., & Burr, D. (2012). When the world becomes “too real”: a Bayesian explanation of autistic perception. *Trends in cognitive sciences*, 16(10), 504–510. doi:10.1016/j.tics.2012.08.009
- Puts, N. A. J., Wodka, E. L., Tommerdahl, M., Mostofsky, S. H., & Edden, R. A. E. (2014). Impaired tactile processing in children with autism spectrum disorder. *Journal of Neurophysiology*, 111(9), 1803–1811. doi:10.1152/jn.00890.2013
- Revelle, W. (1978). ICLUST: A cluster analytic approach to exploratory and confirmatory scale construction. *Behavior Research Methods & Instrumentation*, 10(5), 739–742. doi:10.3758/BF03205389
- Revelle, W. (1979). Hierarchical Cluster Analysis And The Internal Structure Of Tests. *Multivariate Behavioral Research*, 14(1), 57–74. doi:10.1207/s15327906mbr1401\_4
- Riquelme, I., Hatem, S. M., & Montoya, P. (2016). Abnormal Pressure Pain, Touch Sensitivity, Proprioception, and Manual Dexterity in Children with Autism Spectrum Disorders. *Neural Plasticity*, 2016, 1723401. doi:10.1155/2016/1723401
- Robertson, A. E., & David R Simmons, R. (2015). The sensory experiences of adults with autism spectrum disorder: A qualitative analysis. *Perception*, 44(5), 569–586.
- Robertson, A. E., & Simmons, D. R. (2013). The Relationship between Sensory Sensitivity and Autistic Traits in the General Population. *Journal of Autism and Developmental Disorders*, 43(4), 775–784. doi:10.1007/s10803-012-1608-7
- Robic, S., Sonié, S., Fonlupt, P., Henaff, M.-A., Touil, N., Coricelli, G., et al. (2014). Decision-Making in a Changing World: A Study in Autism Spectrum Disorders. *Journal of Autism and Developmental Disorders*. doi:10.1007/s10803-014-2311-7
- Simmons, D., & Milne, E. (2015). Response to Davis and Plaisted-Grant: Low or high endogenous neural noise in autism spectrum disorder? *Autism: The International Journal of Research and Practice*, 19(3), 363–364. doi:10.1177/1362361314557683
- Simmons, D. R., McKay, L., McAleer, P., Toal, E., Robertson, A., & Pollick, F. E. (2007). Neural noise and autism spectrum disorders. *Perception*, 36, 119–120.
- Simmons, D. R., Robertson, A. E., McKay, L. S., Toal, E., McAleer, P., & Pollick, F. E. (2009). Vision in autism spectrum disorders. *Vision research*, 49(22), 2705–2739. doi:10.1016/j.visres.2009.08.005
- Sinclair, D., Oranje, B., Razak, K. A., Siegel, S. J., & Schmid, S. (2016). Sensory processing in autism spectrum disorders and Fragile X syndrome-From the clinic to animal models. *Neuroscience and Biobehavioral Reviews*. doi:10.1016/j.neubiorev.2016.05.029
- Smith, R. S., & Sharp, J. (2013). Fascination and isolation: a grounded theory exploration of unusual sensory experiences in adults with Asperger syndrome. *Journal of Autism and Developmental Disorders*, 43(4), 891–910. doi:10.1007/s10803-012-1633-6
- Sonié, S., Kassai, B., Pirat, E., Bain, P., Robinson, J., Gomot, M., et al. (2013). The French version of the autism-spectrum quotient in adolescents: a cross-cultural validation study. *Journal of Autism and Developmental Disorders*, 43(5), 1178–1183. doi:10.1007/s10803-012-1663-0
- Sonié, S., Kassai, B., Pirat, E., Masson, S., Bain, P., Robinson, J., et al. (2011). [French version of screening questionnaire for high-functioning autism or Asperger syndrome in adolescent: Autism Spectrum Quotient, Empathy Quotient and Systemizing Quotient. Protocol and questionnaire translation]. *Presse Médicale* (Paris, France: 1983), 40(4 Pt 1), e181-188. doi:10.1016/j.lpm.2010.07.016

- Steiger, J. H. (1980). Testing Pattern Hypotheses On Correlation Matrices: Alternative Statistics And Some Empirical Results. *Multivariate Behavioral Research*, 15(3), 335–352. doi:10.1207/s15327906mbr1503\_7
- Takayama, Y., Hashimoto, R., Tani, M., Kanai, C., Yamada, T., Watanabe, H., et al. (2014). Standardization of the Japanese version of the Glasgow Sensory Questionnaire (GSQ). *Research in Autism Spectrum Disorders*, 8(4), 347–353. doi:10.1016/j.rasd.2013.12.017
- Tavassoli, T., & Baron-Cohen, S. (2012). Taste identification in adults with autism spectrum conditions. *Journal of Autism and Developmental Disorders*, 42(7), 1419–1424. doi:10.1007/s10803-011-1377-8
- Tavassoli, T., Hoekstra, R. A., & Baron-Cohen, S. (2014). The Sensory Perception Quotient (SPQ): development and validation of a new sensory questionnaire for adults with and without autism. *Molecular Autism*, 5, 29. doi:10.1186/2040-2392-5-29
- Tavassoli, T., Miller, L. J., Schoen, S. A., Nielsen, D. M., & Baron-Cohen, S. (2014). Sensory over-responsivity in adults with autism spectrum conditions. *Autism: The International Journal of Research and Practice*, 18(4), 428–432. doi:10.1177/1362361313477246
- Van de Cruys, S., de-Wit, L., Evers, K., Boets, B., & Wagemans, J. (2013). Weak priors versus overfitting of predictions in autism: Reply to Pellicano and Burr (TICS, 2012). *i-Perception*, 4(2), 95–97. doi:10.1068/i0580ic
- Van de Cruys, S., Evers, K., Van der Hallen, R., Van Eylen, L., Boets, B., de-Wit, L., & Wagemans, J. (2014). Precise minds in uncertain worlds: Predictive coding in autism. <https://lirias.kuleuven.be/handle/123456789/455945>. Accessed 17 July 2014
- Van de Cruys, S., Van der Hallen, R., & Wagemans, J. (2016). Disentangling signal and noise in autism spectrum disorder. *Brain and Cognition*. doi:10.1016/j.bandc.2016.08.004
- Velicer, W. F. (1976). Determining the number of components from the matrix of partial correlations. *Psychometrika*, 41(3), 321–327. doi:10.1007/BF02293557
- Ward, J., Hoadley, C., Hughes, J. E. A., Smith, P., Allison, C., Baron-Cohen, S., & Simner, J. (2017). Atypical sensory sensitivity as a shared feature between synaesthesia and autism. *Scientific Reports*, 7, 41155. doi:10.1038/srep41155
- Wicker, B., Monfardini, E., & Royet, J.-P. (2016). Olfactory processing in adults with autism spectrum disorders. *Molecular Autism*, 7, 4. doi:10.1186/s13229-016-0070-3
- Zachor, D. A., & Ben-Itzhak, E. (2013). The Relationship Between Clinical Presentation and Unusual Sensory Interests in Autism Spectrum Disorders: A Preliminary Investigation. *Journal of Autism and Developmental Disorders*. doi:10.1007/s10803-013-1867-y

## Synthesis

### GSQ questionnaire

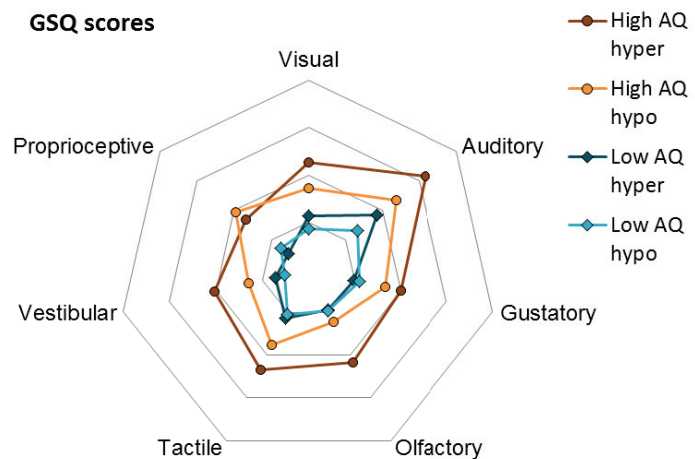
- Validation of the GSQ French version, according to the Universalist model of cross cultural adaptation
- Internal GSQ structure: hyper- vs. hypo-sensitivity ▷ **Clearer in the high AQ group**
- Consistency between GSQ responses ▷ **Greater in the high AQ group**

### Sensory sensitivity

- Strong correlation between the AQ and GSQ scores ▷ **Twice stronger in the high AQ group**
- Hypersensitivity score > hyposensitivity score ▷ **More pronounced in the high AQ group**
- GSQ scores per sensory modality ▷ **Higher in the high AQ group (every modality)**
- Correlation between the 14 GSQ subscales ▷ **Stronger in the high AQ group**  
i.e. more uniform profile of sensitivity

### Implications for ASD

- Relationship between sensory sensitivity and anxiety
- Sensitivity highly depending on the context (Appendix 2)
- Atypical sensitivity enhanced by unpredictability (Appendix 2)
- Refinement of sensory profiles to adapt environments



The presence of both hypersensitivity and hyposensitivity in high AQ and ASD, as well as the testimonies from women with Asperger syndrome (Appendix 2), suggest that the atypical sensory sensitivity in ASD is highly context-dependent and that sensitivity is very often heightened by unpredictable stimuli.

## II. Study II: Atypical learning strategies in ASD

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### *Preamble*

*About Donald: « He had an unusual memory for faces and names, knew the names of a great number of houses. [...] He seemed unable to generalize, transfer an expression to another similar object. »*

*Kanner, 1943*

*« N.P. had many difficulties in primary school. We quickly understood that his teachers were always giving successions of examples and waited for him to discover the underlying rule. His teachers did not say that the aim was to generalize, so, he just learnt everything by heart. Yet, when we told him to look for similarities and helped him a little bit, he often ended up finding them, but it was not so obvious and it remained quite difficult to him. »*

*Father of a participant with ASD (N.P.)*

*« I am very bad at recognizing emotional expressions, even the ones supposed to be easy, like different kinds of smiles. This is true for everyone I meet, except for my wife because I am now a real expert in her smiles. I have managed to remember the smile she had at our wedding where she was very happy, the ones she had during situations where she told me that she felt embarrassed, etc.... Hence, when she smiles, I just have to compare it with the situations we have been in, and I can clearly infer its meaning. It works very well, but simply takes a bit longer than certain persons, I guess. »*

*Participant with ASD (S.K.)*

Constantly surrounded by a highly changing and complex environment, it is mandatory to be able to ignore irrelevant features and changes (random noise) and to extract underlying regularities in the environment (structure). This is helpful to quickly interpret the current stimulation as well as to predict future stimuli. In the example of patient S.K., remembering a list of smiles associated with specific situations rather than an “average” smile could be suboptimal in daily-life (energy and time consuming). However, it can also endow him or people alike with an extraordinary expertise, such as being able to faithfully draw what he could precisely encode in memory. Such an atypical way of learning or memorizing can be detrimental for instance when having to recognize the emotion behind the expression, as well as in many other seemingly trivial daily life situations.

Qian and Lipkin (2012) suggested that the social and non-social symptoms of ASD could be explained by the unbalanced use of two learning styles: the so-called INT and LUT learning styles. INT refers to *interpolation* between examples, enabling to extract the underlying (more abstract) statistical structure. LUT stands for *lookup table* and indicates a strategy that consists in storing each experience precisely, without compressing information through inferring categories. It corresponds, for

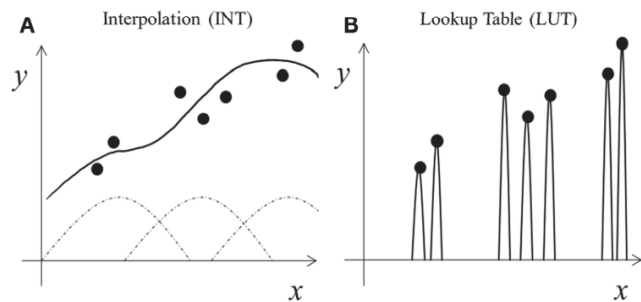
instance, to learning by heart a list of association between phone numbers and names. The LUT style would be characterized by a precise encoding of the sensory inputs, somehow overfitting the information (including irrelevant features). Such an overfitting would impair global processing abilities and prevent from generalizing or categorizing (Figure 35). Indeed, too high prediction errors would thus accompany every new stimulus, irrespectively of whether they match a contextual (global) regularity share by all surrounding stimuli (in space or time) or not.

In their articles, Qian and Lipkin hypothesized that, as compared to neurotypicals (NT), individuals with ASD would make less use of the INT learning strategy, and would present a bias toward the LUT learning strategy.

We decided to test this hypothesis in a new visual task that we designed for that purpose. We were interested in determining whether participants with ASD would (1) spontaneously make less use of an INT learning strategy as predicted by Qian and Lipkin, (2) be able to use the INT and LUT learning strategies just like NT subjects, when explicitly told to do so.

We thus created a set of visual stimuli with two specificities: each stimulus belonged to a category and within this category they shared a common unique feature, but each stimulus was also specific enough to be distinguished from all other stimuli. Hence the stimuli could be either categorized or memorized independently. Importantly, we design the task so that participants could correctly perform half of it using the INT learning strategy, and the other half using the LUT learning strategy. We used a set of new artificial stimuli so as to ensure that subjects would not have prior knowledge over them.

**Figure 35 : Schematic illustration of the INT and LUT learning styles**  
(Qian and Lipkin 2011)



**A. INT learning:** broad tuning functions (dashed curves) are combined (solid curve) to capture the trend of the training data (dots).

**B. LUT learning:** narrow tuning functions are scaled (solid curves) to match each training datum exactly.

## Article

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# Adults with autism tend to undermine the hidden environmental structure: evidence from a visual associative learning task

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### *Abstract*

The learning-style theory of Autism Spectrum Disorders (ASD) (Qian and Lipkin 2011) states that ASD individuals differ from neurotypics in the way they learn and store information about the environment and its structure. ASD would rather adopt a *lookup-table* strategy (LUT: memorizing each experience), while neurotypics would favor an *interpolation* style (INT: extracting regularities to generalize). In a series of visual behavioral tasks, we tested this hypothesis in 20 neurotypical and 20 ASD adults. ASD participants had difficulties using the INT style when instructions were hidden but not when instructions were revealed. Rather than an inability to use rules, ASD would be characterized by a disinclination to generalize and infer such rules.

**Keywords:** autism, perception, categorization, learning, local and global processing

## Introduction

An atypical learning style was mentioned in the very first reports about autism (Asperger 1944; Kanner 1943). Léo Kanner had noticed that children with autism could not learn from adults in “*conventional ways*” (Kanner 1943). For instance, one child with autism had “*an unusual memory for faces and names, knew the names of a great number of houses*”, but “*seemed unable to generalize, transfer an expression to another similar object*” (Kanner 1943). Hans Asperger also described individuals with autism as being poor at “*mechanical learning*” (Asperger 1944; Frith 1991), referring to the learning style spontaneously used by typically developing children.

In Autism Spectrum Disorders (ASD), peculiarities of learning often suggested a failure to adapt rules and to generalize (Dawson et al. 2005; Plaisted 2001). Particularly, many studies have underlined an atypical category learning in ASD, usually slower and less accurate than in neurotypical (NT) participants (Alderson-Day and McGonigle-Chalmers 2011; Carmo et al. 2017; Church et al. 2010, 2015; Gastgeb et al. 2012; Gastgeb and Strauss 2012; Klinger and Dawson 2001; Soulières et al. 2007, 2011; Vladusich et al. 2010). The ability to extract regularities or common features between different stimuli in order to categorize them has often been investigated in ASD by using dot pattern categorization tasks. Studies using such tasks showed different degrees of impairment in children (Church et al. 2010) and adults (Gastgeb et al. 2012) with ASD, (although see Vladusich et al. 2010). Noticeably, individuals with ASD were more impaired than neurotypics to categorize dot patterns that were most distorted from the category prototype (Froehlich et al. 2012). In ASD, studies showed an impaired ability to build up a mental representation of a category (Church et al. 2010; Klinger and Dawson 2001).

Several theories have attempted to explain which mechanisms fail to be used in ASD, yielding atypical perception and learning. The *Reduced generalization model* (Plaisted 2001) suggested that individuals with ASD would have difficulties to extract similarities between stimuli, hence to generalize. Not only should this affect perception, but also social comprehension, as processing the main underlying regularities of social stimuli and situations is necessary to appropriately react to them. More recently, a *learning-style theory* of autism was introduced (Qian and Lipkin 2011), inspired by the observation that individuals with ASD show difficulties to learn based on training examples (Dawson and Mottron 2008). The authors oppose two learning styles: the *interpolation* (INT) and the *lookup-table* (LUT) one.

They suggest that the INT learning-style would be preferentially used by NT individuals, while individuals with ASD would be more biased toward the LUT learning-style.

The INT learning style consists in extracting underlying regularities or hidden rules from the environmental structure, in order to generalize and categorize. Generalization would stem from the ability to interpolate across gaps between examples, in a context where examples could be encoded with broad tuning functions (i.e. with low precision). In contrast, the LUT learning style consists in storing each experience precisely without properly compressing information (e.g. learning an association of names and phone numbers). Storing examples with narrow tuning functions (i.e. with high precision) would prevent from making interpolations but would help distinguishing each example from one another. Fitting each example very precisely becomes a waste of resources in a noisy environment where details are meaningless. In contrast, the INT learning style is context-dependent and particularly efficient in noisy environments, since encoding stimuli with broad tuning functions enables the categorisation and interpretation of new stimuli. In other words, contrary to the LUT learning style, the INT one prevents from overfitting and would thus be more adapted to real-life situations where all kinds of noise have to be filtered out. This is essential to correctly interpret sensory stimuli, and subsequently to elaborate functions such as language (Fisher et al. 2014; Marcus et al. 2007) or appropriate social skills (Weston and Turiel 1980). Social stimuli are particularly noisy, flexible and context-dependent, and their multidimensional and complex underlying regularities need to be interpolated between situations.

A wide variety of atypical behaviors in ASD could be explained by a reduced use of the INT style and a greater use of the LUT style (as compared to NT). For instance, some persons with ASD report that they tend to learn each situation almost by rote (LUT style) instead of generalizing (INT style). Temple Grandin explained: *“When I encounter a new social situation, I have to search my memory for a similar experience that I can use as a model for my next action. [...] For common social interactions with clients I use preprogrammed, prerehearsed responses”* (Grandin 1997). With the LUT style, accumulating a great number of examples would end up increasing the potential match between present and past situations, but is highly demanding and can be saturated. A reduced use of the INT style in ASD would also be in line with findings on categorization and prototype formation suggesting impaired generalization (Church et al. 2010; Gastgeb et al. 2012; Scherf et al. 2008; Vladusich et al. 2010). Yet, some results on categorization in ASD remain inconsistent regarding the degree of impairment (e.g. Soulières et al. 2007; Vladusich et al. 2010), and the ability to categorize in real-life ecological situations (where individuals with ASD are not



given instructions) might differ from the situations of experimental testing described in scientific reports.

In the present study, we designed and tested a new visual paradigm questioning whether ASD individuals would indeed make less use of the INT style and more use of the LUT styles than NT. Our paradigm matched the recommendation by Qian and Lipkin (2011) suggesting that age- and IQ-matched NT and ASD participants needed to be “*trained on random (but fixed) association tasks and tasks with hidden, underlying rules*”, and that it was “*best to use non-social tasks (e.g. learning visual categorization of shapes) to avoid potential confounds from autistic and typical subjects’ different developmental and intervention histories*”.

We aimed at determining which strategy was *spontaneously* favored by NT and ASD participants, respectively. Precisely, we investigated whether adults with ASD would preferentially look for a rule based on general features of the presented items (INT style), or would rather try to memorize all items independently and precisely (LUT style). Participants first performed a series of tasks. Importantly, they received no instructions as to which learning strategy would be more successful. In these tasks, the hidden structures relied on INT and/or LUT learning-styles. Afterwards, participants fulfilled questionnaires to explicitly report the learning strategies they had tried to instantiate. Later on, they performed similar tasks but with clear instructions about the strategy to favor. These tasks were meant to control for their abilities to implement the various learning styles when explicitly told to do so.

## ***Material and Methods***

### ***Participants***

Twenty-two participants with ASD and 23 NT participants took part in the study. Two participants with ASD and three NT participants were discarded from the main analysis as they failed at performing the control task (see Results section). The two resulting groups consisted of 20 participants with ASD (mean age in years:  $33.6 \pm 10.0$ ) and 20 NT participants (mean age in years:  $30.8 \pm 6.9$ ). The two groups were matched for age, gender ratio, education level, and intellectual quotient assessed by the Wechsler Adult Intelligence Scale (WAIS III or IV). Their characteristics are detailed in Table 1. All participants completed the autism-spectrum quotient (AQ) test (Baron-Cohen et al. 2001). Patients with ASD were diagnosed by clinicians using criteria defined in the *Diagnostic and Statistical Manual of Mental Disorders*

(4<sup>th</sup> or 5<sup>th</sup> edition: *DSM–IV or V*; American Psychiatric Association) and confirmed by a psychiatrist specialized in ASD. The *Autism Diagnostic Observation Schedule* (14 patients), the *Adult Asperger Assessment* (five patients) and/or *Autism Diagnostic Interview* (four patients) were used to objectively screen for ASD. All patients had a diagnosis of ASD without any intellectual deficiency or language acquisition delay. Participants had normal or corrected-to-normal vision. NT participants reported no history of neurological or psychiatric disorders.

Approval was obtained from the local ethics committee (French South East IV Committee for the Protection of Persons). Participants gave their written consent beforehand.

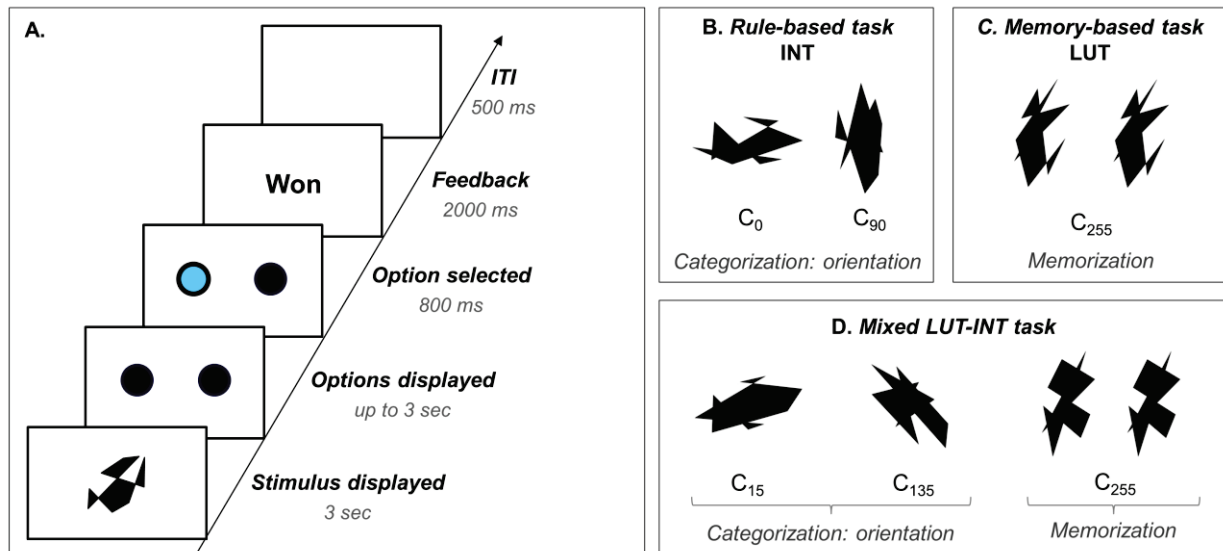
	NT group	ASD group	p	
<b>Number</b>	20	20	<i>ns</i>	<b>Table 1: Demographical and neuropsychological characteristics of the participants</b> Values correspond to the group mean ( $\pm$ standard deviation). The p-values obtained from the t-test comparing the two groups are shown in the right column. <i>ns</i> : no significant difference between the two groups at Student t-test. Educational level: number of years of study after Baccalaureate. AQ: Autism-spectrum quotient. * For six of the ASD participants, mean IQ score could not be computed as the four subscores of the WAIS were too heterogeneous to be averaged.
<b>Male / Female</b>	15 / 5	16 / 4	<i>ns</i>	
<b>Age (years)</b>	30.8 ( $\pm$ 6.9)	33.6 ( $\pm$ 10.0)	<i>ns</i>	
<b>Educational level (years)</b>	4.6 ( $\pm$ 2.6)	3.4 ( $\pm$ 2.8)	<i>ns</i>	
<b>WAIS IV</b>				
<i>Verbal comprehension</i>	124 ( $\pm$ 13)	123 ( $\pm$ 18)	<i>ns</i>	
<i>Perceptual reasoning</i>	111 ( $\pm$ 14)	113 ( $\pm$ 17)	<i>ns</i>	
<i>Working memory</i>	112 ( $\pm$ 11)	107 ( $\pm$ 20)	<i>ns</i>	
<i>Processing speed</i>	111 ( $\pm$ 16)	105 ( $\pm$ 25)	<i>ns</i>	
<i>Mean score*</i>	119 ( $\pm$ 13)	119 ( $\pm$ 22)	<i>ns</i>	
<b>AQ score</b>	12 ( $\pm$ 6)	35 ( $\pm$ 8)	$<10^{-6}$	

## Stimuli

We created visual stimuli that were unique and distinguishable enough to be memorized independently, but could also be categorized based on common features. Importantly, these stimuli were new to all participants, so as to avoid any influence from prior knowledge. All stimuli were created using Matlab 2013a.

Each stimulus consisted of a geometric picture defined by lines and angles that formed a shape. It was made of nine points pseudo-randomly chosen on a horizontal ellipse and then connected with each other. The resulting pattern was filled with black color. Then, 104 of the ellipses were rotated by 15° [9:21], 32 by 90° [84:96], 104 by 135° [129:141], 32 by 255° [249-261] and 32 by 0° [-6:6] (Figure 1). These rotations enabled the formation of five

categories of geometrical pictures:  $C_0$ ,  $C_{15}$ ,  $C_{90}$ ,  $C_{135}$ ,  $C_{255}$ . We added a Gaussian noise to the orientation within each category with a standard deviation of  $\pm 6^\circ$  in order to assess whether this would affect performance.



**Figure 1: Typical trial (left) common to most of tasks (right)**

- A. Example of trial presentation. This structure was the same in every task, except for the Recognition test. ITI: inter trial interval.
- B. The Rule-based task tested the spontaneous use of the INT strategy. Stimuli were oriented along  $0^\circ$  (category  $C_0$ ) or  $90^\circ$  (category  $C_{90}$ ) and each stimulus only appeared once. Stimuli had to be categorized according to their orientation.
- C. The Memorization-based task tested the spontaneous use of the LUT strategy. Stimuli were all oriented along  $255^\circ$  (category  $C_{255}$ ) and were repeated eight times each. The stimulus / winning response association had to be memorized.
- D. In the Mixed LUT-INT task,  $C_{15}$  and  $C_{135}$  stimuli had to be classified according to their orientation and were never repeated, whereas  $C_{255}$  stimuli had to be memorized and appeared 16 times each.

## Behavioral tasks

### General procedure

Participants were sitting at 60cm from the computer screen and the displayed stimuli were 20cm long and 8cm wide. Subjects responded with their dominant hand, using the two buttons of the computer mouse. The experiments were programmed using the software package Presentation (Neurobehavioral Systems).

Participants were told that they were going to perform a series of visual tasks in which the goal was to win as many points as possible. They were explained that each stimulus was predictive of the correct choice to be made (left or right) in order to be successful. In each trial, after button press, participants received feedback (“Won”: 1 point, “Lost”: 0 point). The

feedback would give them the possibility to discover a strategy in order to win more points. They also knew that the link between the stimulus and the winning answer would be different from one task to another. Importantly and hidden from the participants, each stimulus-winning-response association was either consistent with a rule-based approach (INT) or not. In the former, applying a memorization-based (LUT) strategy would be suboptimal, while in the latter it would become the best (and only possible) strategy.

At each trial, a stimulus was displayed on a white screen for three seconds, and followed by two identical black discs indicating the two possible answers (Figure 1-A). Participants were given three seconds at most to select one of the two options. The disc on the side chosen by the participant was then colored in blue for 800ms to highlight their selection. Immediately after, a feedback was given to indicate whether their choice was correct or not (“Won” or “Lost” displayed on the screen for 2000ms). The inter-stimulus interval consisted of a white screen displayed for 500ms. In each task, there were no more than five consecutive trials with the same winning response, and the same stimulus never appeared twice consecutively. Participants were asked to favor accuracy over speed.

Participants completed six tasks, and the whole experiment lasted for about one hour. The order of the tasks was the following: 1<sup>st</sup> (or 2<sup>nd</sup>): *Rule-based task*, 2<sup>nd</sup> (or 1<sup>st</sup>): *Memorization-based task*, 3<sup>rd</sup>: *Mixed LUT-INT task*, 4<sup>th</sup>: *Recognition test*, 5<sup>th</sup> (or 6<sup>th</sup>): *Rule-based control task*, 6<sup>th</sup> (or 5<sup>th</sup>): *Memorization-based control task*.

### **1. *Rule-based task, without instructions (INT)***

This task assessed the spontaneous use of the INT learning-style. Participants were only told that the displayed stimulus was informative about the side of the winning response. The hidden associative rule was such that the correct response depended on stimulus orientation (Figure 1.B). Two categories of stimuli were presented: C<sub>0</sub> (32 different horizontal shapes) and C<sub>90</sub> (32 different vertical shapes). The stimulus-winning-response association was counter-balanced over participants. For half of the subjects, a correct left button press (resp. right) was associated with horizontal stimuli (resp. vertical) and the reverse rule applied for the other half. As each stimulus was never presented twice, this association could not be memorized. The *Rule-based task* consisted of 64 trials, and lasted for six minutes on average.

### **2. *Memorization-based task, without instructions (LUT)***

This task assessed the spontaneous use of the LUT learning-style. Participants were only told that there was a link between the stimulus displayed and the side of the winning

response. To succeed, participants had to memorize a unique association between a stimulus and a response side (Figure 1.C). Eight stimuli from category  $C_{255}$  were pseudo-randomly presented eight times each. Four of them were associated with a left winning answer, whereas the four others were associated with a right winning answer. Associations were counter-balanced over participants. This *Memorization-based task* consisted of 64 trials, and lasted for six minutes on average.

We counterbalanced the order of presentation of the *Rule-based task* and *Memorization-based task* between participants.

### 3. *Mixed LUT-INT task, without instructions (LUT and INT)*

This task tested the spontaneous use of both the LUT and INT learning strategies. Again, participants were told that there was a link between the stimulus displayed and the side of the winning response. They were also told that if they had discovered strategies during the two previous tasks (*Rule-based* and *Memorization-based tasks*), these could be useful for this new task. To succeed, participants had to use the INT strategy for half of the stimuli (categorization), and the LUT strategy for the other half (memorization) (Figure 1.D). This task was divided into four sessions consisting of 64 trials each. In each session, 32 stimuli had to be classified according to their orientations (16 belonging to  $C_{15}$ , and 16 belonging to  $C_{135}$ ) and 8 stimuli belonging to  $C_{255}$  were displayed four times each and had to be memorized. The four sessions presented a total of 64 stimuli from  $C_{15}$  (each presented once), 64 stimuli from  $C_{135}$  (each presented once), and 8 stimuli from  $C_{255}$  (each presented 16 times). This *Mixed LUT-INT task* consisted of 256 trials in total, and lasted for about 24 minutes (interrupted by two-minute breaks in-between sessions).

### 4. *Recognition test*

This task tested whether participants did memorize some of the stimuli presented during the *Mixed LUT-INT task*, performed right beforehand. Note that this is different from having memorized the association between a given stimulus and the side of the winning response for that stimulus. Participants were presented with stimuli displayed during the *Mixed LUT-INT task* or never displayed before, and they had to indicate by a button press whether they had already seen them or not.

Sixteen stimuli from each of the three following categories were used:  $C_{15}$ ,  $C_{135}$  and  $C_{255}$  (48 stimuli in total). Within each category, eight stimuli had been displayed during the *Mixed LUT-INT task*, while the eight others were new. Each stimulus appeared for three

seconds, and participants had to press on the side of the screen indicating “*seen*” or “*never seen*” (this side was counterbalanced between participants). No feedback was provided, and the inter-stimulus trial lasted for 800ms. The *Recognition test* consisted of 48 trials, and lasted for about 4 minutes.

### **5. *Rule-based control task, with instructions (INT)***

This task measured the participants’ performance when explicitly told that stimuli presenting with the same orientation were associated with the same winning side, and that there were two classes of orientations. Prior to the task, participants were also shown two stimulus examples illustrating the two different orientations. The design of this control task was the same as in the main *Rule-based task*. Two categories of stimuli were presented: 32 stimuli belonging to  $C_{15}$  (e.g., associated with a right winning response), and 32 belonging to  $C_{135}$  (e.g., associated with a left winning response). The side of the winning response was counter-balanced between participants. The *Rule-based control task* consisted of 64 trials, and lasted for six minutes on average.

### **6. *Memorization-based control task, with instructions (LUT)***

This task measured the participants’ performance when explicitly told to memorize the stimulus-winning-response association.

The design of this control task was the same as in the main *Memorization-based task*. Eight stimuli belonging to  $C_{255}$  were pseudo-randomly presented eight times each (these were different from the ones presented in the previous tasks). Half of the stimuli were associated with a right winning answer, and the other half with the left winning answer. The side of the winning answer was counter-balanced between participants. The *Memorization-based control task* consisted of 64 trials, and lasted for six minutes on average.

## **Questionnaires**

After the fourth task (before starting the control tasks), participants completed a questionnaire. They were asked to report the strategies they tried to use for each task. We classified answers to the question “Can you describe the strategy you used for each of the exercises?” within four categories: categorization based on the orientation, on another rule based on global stimulus features (e.g.: large vs. small colored surface), on a rule based on local stimulus features (e.g.: side of the smallest angle of the shape), or on memorization. Participants were also asked to estimate their concentration level (on a scale from 0 to 2, with

2 corresponding to “*very concentrated*”). Finally, they were asked to indicate whether they memorized some of the stimuli in each task, and to indicate which kind of memory they thought they were best at (visual, auditory, kinesthetic, or other).

### ***Statistical analyses***

Between-group comparisons of the demographical data and scores at neuropsychological tests were performed using Student’s t-test. The accuracy corresponds to the average percentage of correct answers in each task. In the *Memorization-based, Rule-based*, and control tasks, accuracies and response times were compared between groups using Student t-tests. In the *Mixed LUT-INT* task, a three-way analysis of variance (ANOVA) was applied on accuracies to assess the effect of group (NT or ASD), stimulus type (INT or LUT) and sessions (1 to 4). Student’s t-tests were used for post-hoc comparisons.

Correlations between accuracies or response times and AQ scores were examined using Pearson analysis. Correlation coefficients were compared using Fisher r-to-z transformation.

Chance levels were calculated as the upper limit of the confidence interval in binomial tests assessing 50% of success (with a confidence level of 0.95) i.e. 68.1% of correct answers for 32 trials, 62.8% for 64 trials, 59.0% for 128 trials, and 56.3% for 256 trials. Proportions of participants scoring above chance level were compared using proportion tests. Proportions of participants reporting different strategies in the questionnaires were compared between groups using proportion tests.

Statistical analyses were performed using R (<http://www.R-project.org>). The threshold for statistical significance was always set to  $p < .05$ .

## ***Results***

No effect of orientation blurring within each stimulus categories could be observed on accuracy. Hence all the results reported below integrate over this dimension.

Besides accuracy, we also analyzed reaction times which we only report here whenever the group difference proved significant.

### ***Participant selection criteria in the control tasks***

The *Rule-based control* task was used to select participants for further analysis. We excluded the participants that were not able to categorize the stimuli according to their

orientations when they were explicitly asked to. We considered this ability as a prerequisite to perform the implicit *Rule-based* and *Mixed LUT-INT* tasks. Hence, participants who did not obtain more than two third of correct answers at this control task were excluded from our analyses. Three NT participants (mean accuracy: 56.8%  $\pm$ 14.0) and two ASD participants (mean accuracy: 53.9%  $\pm$ 3.3) were excluded. These participants reported that they did not manage to identify any global orientation in the displayed stimuli, apart from one of the ASD participant who reported that he recognized the orientation but could not help pressing the left button.

The resulting groups consisted of 20 NT and 20 ASD participants whose characteristics are given in Table 1.

### ***Rule-based control task (with instructions)***

NT and ASD participants reached 98.4% ( $\pm$ 1.9) and 95.2% ( $\pm$ 6.3) of correct answers, respectively (Figure 2-A). 100% of participants in each group scored above chance level. Although accuracy was very high in both groups, this difference was significant in favor of NT participants ( $p = .04$ ). After more detailed analyses of error repartition, this difference appeared to be mostly driven by differences during the first trials. ASD participants committed twice more errors than NT participants between the 1<sup>st</sup> and 6<sup>th</sup> trial.

### ***Memorization-based control task (with instructions)***

The NT and ASD groups obtained 66.6% ( $\pm$ 9.8) and 61.9% ( $\pm$ 14.5) of correct answers, respectively. No differences in accuracy were found between the two groups, and both groups scored at chance level (Figure 2-B). In the NT and ASD groups, 60% and 55% of the participants scored above chance level, respectively (no group difference).

NT subjects answered faster than ASD ones (NT: 1857ms  $\pm$ 625 vs. ASD: 2465ms  $\pm$ 1025,  $p < .05$ ).

### ***Comparison of the two control tasks***

The two groups were less accurate in the *Memorization control* task than in the *Categorization control* task ( $p < 10^{-6}$  in both groups).

### ***Rule-based task (without instructions)***

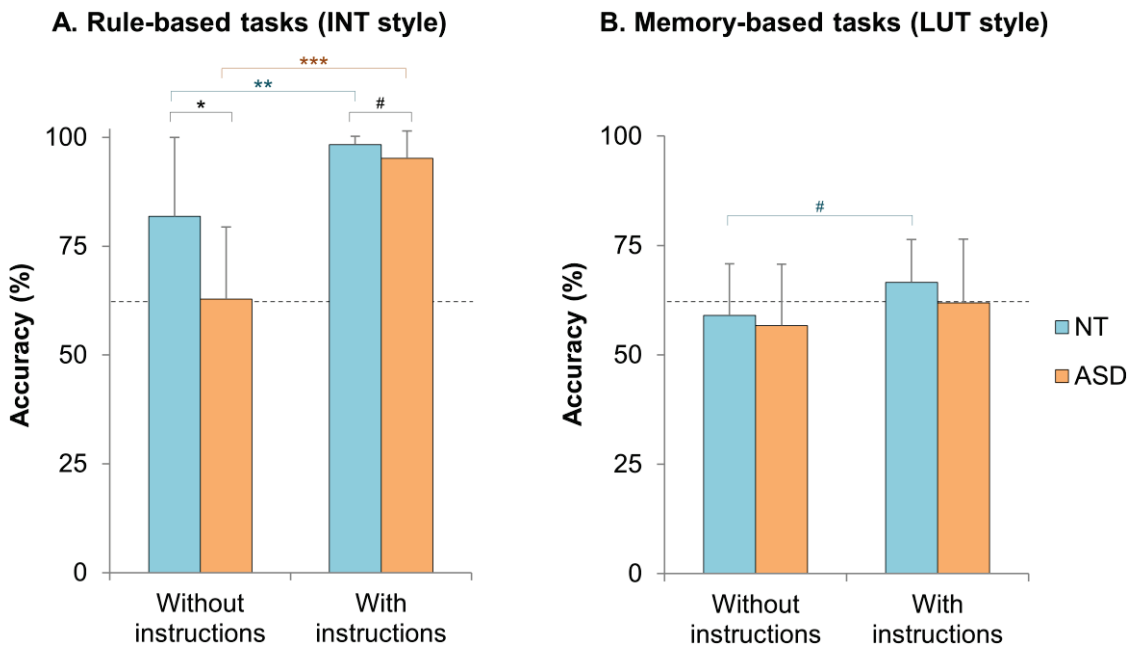
The NT group performed better than the ASD group ( $p < .01$ ), with 81.9% ( $\pm$ 18.1) versus 62.8% ( $\pm$ 16.6) of correct answers (Figure 2-A). The NT group answered faster than the ASD group (NT: 1670ms  $\pm$ 1043 vs. ASD: 2663ms  $\pm$ 1113,  $p < .01$ ), in particular for correct answers (NT: 1605ms  $\pm$ 1055 vs. ASD: 2636ms  $\pm$ 1113,  $p < .01$ ). A higher proportion of NT



participants scored above chance level, as compared to ASD participants (NT: 75% vs. ASD: 30%,  $p < .05$ ). As another indicator of group difference in inferring and applying the rule, in the NT group 85% of the participants answered correctly eight times in a row after only 16 trials (median). In contrast, in the ASD group, only 30% of the participants reached the same performance but after 27 trials (median).

### **Memorization-based task (without instructions)**

The NT and ASD groups obtained 59.0% ( $\pm 11.8$ ) and 56.6% ( $\pm 14.0$ ) of correct answers, respectively (Figure 2-B). No differences in accuracy were found between groups, and both groups scored at chance level on average. 40% of the NT and 30% of the ASD participants scored above chance level (no group difference).



**Figure 2: Accuracy in the Rule-based and Memorization-based tasks**

- A. Group mean accuracy observed in the Rule-based task without (left) and with instructions (right, control task).
- B. Group mean accuracy observed in the Memorization-based task without (left) and with instructions (right, control task).

NT group: blue, ASD group: orange. Error bars correspond to standard deviations. The dash line indicates the chance level. #  $p < .05$ , \*  $p < .01$ , \*\*  $p < .001$ , \*\*\*  $p < .0001$ .

### **Comparison between the Rule-based and Memorization-based tasks**

The NT group showed greater accuracy ( $p < 10^{-5}$ ) and shorter response times ( $p < .01$ ) in the *Rule-based* task than in the *Memorization-based* task. Moreover, in the NT group, accuracy in the *Rule-based* task correlated with accuracy in the *Memorization-based* one ( $r = .29$ ,  $p < .05$ ). In contrast, in the ASD group, there was no significant difference between the

accuracy in these two tasks. And accuracy in the *Rule-based* task did not correlate with accuracy in the *Memorization-based* one ( $r = .13, p > .05$ ).

### ***Comparison between the tasks with and without instructions***

In the *Rule-based* tasks, giving instructions resulted in an increase in accuracy of 16.5% ( $\pm 18.4$ ) in the NT group, and of 31.9% ( $\pm 15.7$ ) in the ASD group. Both groups scored significantly higher in the *Rule-based control* task than in the task without instructions (NT:  $p < .001$ , ASD:  $p < 10^{-6}$ ) (Figure 2.A).

In the *Memorization-based* tasks, giving instructions resulted in an increase in accuracy of 7.6% ( $\pm 12.3$ ) in the NT group and of 5.2% ( $\pm 16$ ) in the ASD group. The NT group scored significantly higher in the *Memorization-based control* task than in the task without instructions ( $p < .05$ ), contrary to the ASD group ( $p > .05$ ) (Figure 2.B).

This gain in accuracy following instructions was higher in the ASD group than in the NT group in the *Rule-based* tasks ( $p < .01$ ) but not in the *Memorization-based* tasks.

### ***Mixed LUT-INT task (without instructions)***

Results from the *Mixed LUT-INT* task are shown on Figure 3. A nested ANOVA investigating the effect of group (NT and ASD), stimulus (INT and LUT) and session (1 to 4) on accuracy revealed a significant group effect ( $F(38,1) = 7, p < .01$ ), stimulus effect ( $F(38,1) = 43, p < 10^{-6}$ ) and session effect ( $F(38,3) = 17, p < 10^{-6}$ ). In addition, it showed a significant interaction between group and stimuli ( $F(38,1) = 20, p < 10^{-4}$ ). No significant interactions were found between group and session, between session and stimuli, and between group x session x stimuli.

Post-hoc tests showed that on average, the NT group performed better than the ASD group (NT: 71.3%  $\pm 11.2$  vs. ASD: 62.3%  $\pm 13.4, p < .05$ ). On average, accuracy for INT stimuli was higher than for LUT stimuli (INT: 72.9%  $\pm 18.1$  vs. LUT: 60.7%  $\pm 12.8, p < .001$ ). The NT group scored higher for INT stimuli than the ASD group (NT: 81.5%  $\pm 16.4$  vs. ASD: 64.3%  $\pm 19.9, p < .01$ ), but not differently for LUT stimuli (NT: 61.1%  $\pm 15.8$  vs. ASD: 60.4%  $\pm 15.8$ ). In the NT group, post-hoc tests on the session effect showed a significant increase in accuracy between the first and second/third/fourth sessions ( $p < .001$ ), and between the second and third/fourth sessions ( $p < .05$ ), but no difference between the third and fourth sessions ( $p = .08$ ). In the ASD group, there was only a significant increase in accuracy between the first and third/fourth sessions ( $p < .05$ ).

Within group, the NT scored higher for INT than LUT stimuli ( $p < .001$ ). In the ASD group, no significant difference in accuracy was found between INT and LUT stimuli.

A greater proportion of NT participants scored above chance level for INT stimuli (NT: 90% vs. ASD: 40%,  $p < .001$ ). An equivalent proportion of NT and ASD participants scored above chance level for LUT stimuli (NT: 55% vs. ASD: 50%).

To determine which learning style was associated with the highest accuracy, we compared accuracy for the INT and LUT stimuli for each participant. In the NT group, 85% of the participants obtained higher scores with INT stimuli, and 15% with LUT stimuli. In the ASD group, 30% obtained higher scores with INT stimuli, 50% with LUT stimuli, and 20% showed no difference between the two (i.e. a difference in accuracy smaller than 3%). Group comparisons revealed a higher proportion of NT than ASD participants with higher scores for INT stimuli ( $p < .001$ ), and a higher proportion of ASD than NT participants with higher scores for LUT stimuli ( $p < .05$ ).

### **Correlations with IQ scores**

As the perceptual reasoning score (IQ-PR) includes 3D visual search, we expected accuracy in the *Rule-based* and *Mixed LUT-INT* tasks to correlate with it. It proved to be the case for NT participants only, in the *Rule-based* task ( $r = .60$ ,  $p < .01$ ). And only NT participants showed a non-significant trend in the *Mixed LUT-INT* task ( $r = .43$ ,  $p = .056$ ).

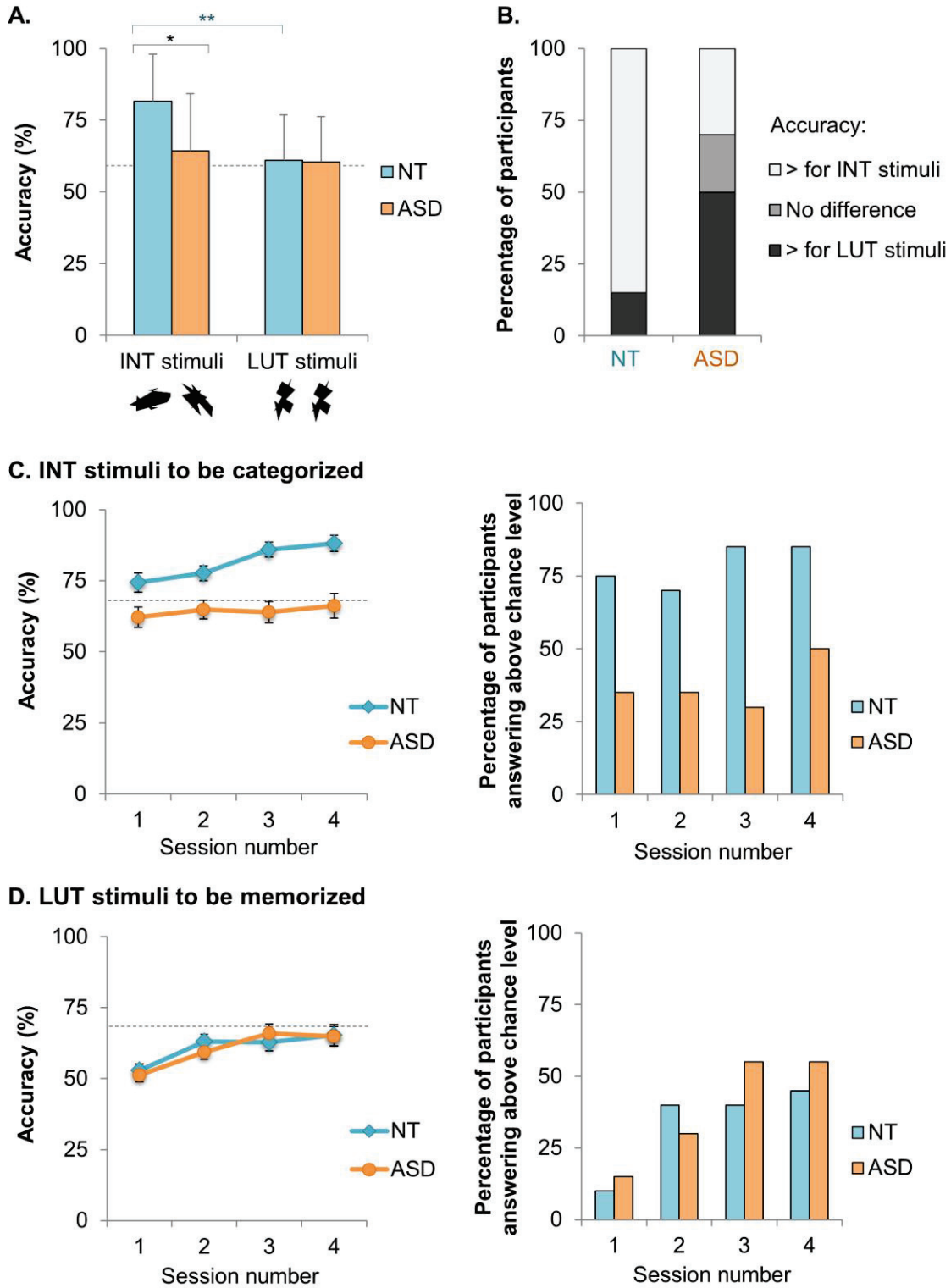
The working memory score (IQ-WM) was expected to correlate with accuracy in the *Memorization-based* and *Mixed LUT-INT* tasks, as it includes attention and concentration abilities. This proved to be the case for NT participants only, in the *Memorization-based* task ( $r = .49$ ,  $p < .05$ ). And both groups showed a non-significant trend in the *Mixed LUT-INT* task (NT:  $r = .43$ ,  $p = .058$ ; ASD:  $r = .46$ ,  $p = .057$ ).

### **Correlations with AQ scores**

The AQ negatively correlated with the overall accuracy obtained with INT stimuli in the *Rule-based task* without instructions ( $r = -.43$ ,  $p < .01$ ) and in the *Mixed-LUTINT task* without instructions ( $r = -.40$ ,  $p < .05$ ), but not in the *Rule-based control task* with instructions. Yet, these correlations were not significant within groups.

The AQ was not correlated with the level of accuracy obtained with LUT stimuli, whatever the task.

Within group, the bias toward the LUT style, measured as the difference in accuracy between the performance with the LUT and INT stimuli in tasks with no instructions did not correlate with AQ either.



**Figure 3: Accuracy in the Mixed LUT-INT task**

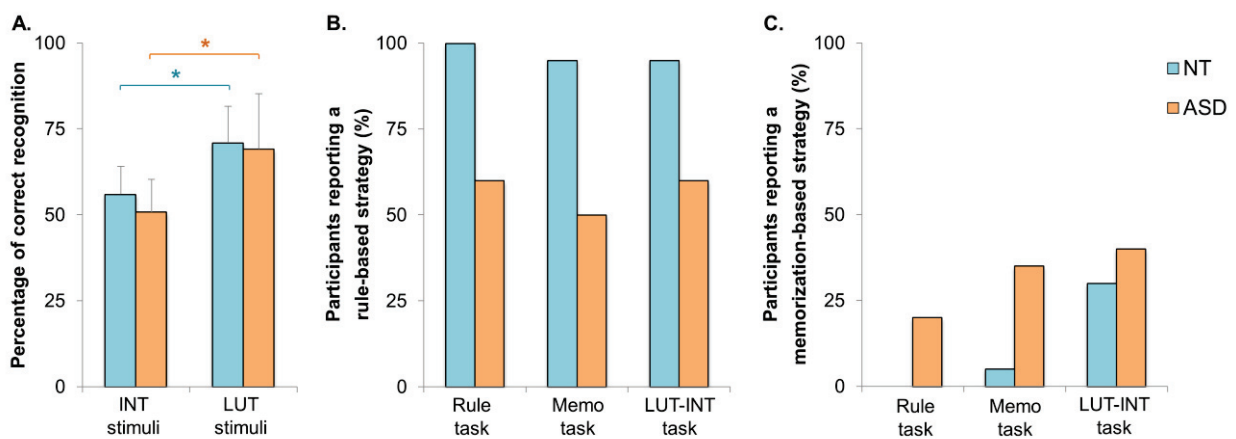
- A. Mean accuracy in the Mixed LUT-INT task for INT stimuli to be categorized (left) and LUT stimuli to be memorized (right).
- B. Percentages of participants with a higher accuracy for INT stimuli than LUT stimuli (clear grey), with a higher accuracy for LUT stimuli than INT stimuli (black), or with no difference in accuracy between INT and LUT stimuli (grey).
- C. Results for INT stimuli across sessions: mean accuracy (left) and percentage of participants answering above chance level (right).

D. Results for LUT stimuli across sessions: mean accuracy (left) and percentage of participants answering above chance level (right).

Error bars correspond to the standard deviation in A and to the standard error of the mean in C and D. The dash line corresponds to the chance level. \*  $p < .01$ , \*\*  $p < .001$ .

### Recognition test

In the *Recognition test*, the two groups performed as accurately (NT: 60.9%  $\pm$ 8.2, ASD: 56.9%  $\pm$ 9.5) and as quickly (NT: 1982ms  $\pm$ 352, ASD: 2163ms  $\pm$ 573). This test aimed at assessing whether the participants had memorized the stimuli that needed to be categorized according to their orientation ( $C_{15}$  and  $C_{135}$ ), and/or the stimuli for which the association with a winning response side needed to be memorized ( $C_{255}$ ). No differences were found between groups for the stimuli belonging to  $C_{15}$  (NT: 50.9%  $\pm$ 10.6, ASD: 46.9%  $\pm$ 16.2),  $C_{135}$  (NT: 60.9%  $\pm$ 13.1, ASD: 54.7%  $\pm$ 12.6) and  $C_{255}$  (NT: 70.9%  $\pm$ 13.9, ASD: 69.1%  $\pm$ 14.3) (Figure 4-A). Both groups remembered more accurately stimuli belonging to  $C_{255}$  (to be memorized) than those belonging to  $C_{15}$  and  $C_{135}$  (to be categorized) (NT:  $p < 10^{-4}$ , ASD:  $p < .001$ ).



**Figure 4: Recognition test and questionnaire results**

A. Percentage of correct answer in the Recognition test, for INT stimuli ( $C_{15}$  and  $C_{135}$ ) and LUT stimuli ( $C_{255}$ ).

B-C. Percentage of participants who reported having used a rule-based strategy (B) or a memorization-based strategy (C) to perform the Rule-based task, Memorization-based task, and Mixed LUT-INT task (these tasks were performed without instructions). Participants could report both strategies for a unique task.

Error bars correspond to standard deviations. \*  $p < .01$

### Post-experiment questionnaires

As compared to ASD participants, a higher proportion of NT participants reported using the rule based on orientation in the *Rule-based* task (NT: 80% vs. ASD: 35%,  $p < .01$ ), and *Mixed LUT-INT* task (NT: 85% vs. ASD: 40%,  $p < .01$ ). In general, a higher proportion of

NT participants reported searching for a rule in the *Rule-based* task (NT: 100% vs. ASD: 60%,  $p < .01$ ), as well as in the *Memorization-based* task (NT: 95% vs. ASD: 50%,  $p < .01$ ), and in the *Mixed LUT-INT* task (NT: 95% vs. ASD: 60%,  $p < .05$ ) (Figure 4-B). In the *Memorization-based* task, a higher proportion of ASD participants tried to memorize the stimuli as compared to NT participants (ASD: 35% vs. NT: 5%,  $p < .05$ ) (Figure 4-C).

In the NT group, a large majority of participants reported using the orientation rule rather than a memorization strategy in the *Rule-based* task (80% vs. 0%,  $p < 10^{-5}$ ), as well as in the *Mixed LUT-INT* task (85% vs. 30%,  $p < .001$ ). In contrast, in the ASD group, a majority of participants reported using a memorization strategy rather than the orientation rule in the *Memorization-based* task (35% vs. 0%,  $p < .05$ ).

The two groups reported similar concentration levels (NT: 1.5/2, ASD: 1.1/2). An equivalent proportion of participants reported having a better “*visual memory*” (NT: 70%, ASD: 79%,  $p > .05$ ). Finally, in each group, a non-significantly different proportion of participants noticed that some stimuli were repeated during the *Memorization-based* task (NT: 90%, ASD: 60%,  $p > .05$ ) and the *Mixed LUT-INT* task (NT: 90%, ASD: 80%,  $p > .05$ ).

Remarkably, the two ASD participants with the best accuracy for INT stimuli in the *Mixed LUT-INT task* reported an alternative strategy to the one based on orientation. They classified the stimuli based on a single detail: given that the stimuli were angled, the highest point of the shape was on the right side of the screen for stimuli belonging to  $C_{15}$  and on the left side of the screen for stimuli belonging on  $C_{135}$ . These two participants declared clicking on the side of this highest point to succeed. Hence, even though they had not noticed the global orientation of the stimuli, they managed to classify the stimuli using a detail-based rule. They were the only two participants who reported having found this rule.

## Discussion

The goal of the present study was to investigate the spontaneous tendency of NT and ASD adults to use two kinds of learning styles: extracting regularities to interpolate between items (INT style) or memorizing lists of associations independently and precisely (LUT style). We had hypothesized that the ASD group would show a bias toward a decreased use of the INT style and an increased use of the LUT style, as compared to NT subjects (Qian and Lipkin 2011). Two main results were in favor of this hypothesis: ASD participants were less inclined to spontaneously use the INT style and reported an increased tendency to use the

LUT style. Importantly though, the ASD group was able to instantiate the INT style when instructed to do so.

### ***Decreased use of the INT style and increased use of the LUT style in ASD***

In ASD, the reduced use of the INT style was confirmed by lower scores in tasks without instructions and by qualitative reports, while the tendency to favor the LUT style was confirmed by qualitative reports only.

In the Rule-based task without instructions and in the Mixed LUT-INT task, ASD participants had difficulties extracting the underlying regularities of the stimuli to find a rule. This could be explained by an increased focus on details of the stimuli preventing them from finding the global rule, and by a reduced tendency to spontaneously look for rules. In addition, a slower dynamic to identify the category and to learn the rule could contribute to a reduced accuracy in these tasks. Slower category learning in ASD could also explain the slight group differences found in the Rule-based control task with instructions, which could be explained by the first trials. Slower category learning was previously evidenced in individuals with ASD (Bott et al. 2006; Gastgeb and Strauss 2012; Soulières et al. 2011). Interestingly, the study by Soulières and colleagues showed that in the early phases of training, ASD participants did not use any identifiable strategies, but they ended up using the same strategies as NT at the end of the training (Soulières et al. 2011).

Besides, Qian and Lipkin (2011) had hypothesized that individuals with ASD would perform better with the LUT style in tasks where participants would have to learn random and rigid associations. No group difference in accuracy was found for the LUT style, neither in the explicit nor in the implicit conditions. This reveals that this task was actually difficult for all participants, and it is possible that group differences might have emerged if a longer period of learning had been proposed. Yet, qualitative reports revealed that the ASD group tended to try to memorize stimuli more than NT participants did. In the Mixed LUT-INT task, a limitation to the use of the LUT style might have been that participants first needed to identify that there were three categories of stimuli to be able to target and memorize stimuli from category C255 only. Indeed, three ASD participants spontaneously reported that they tried to memorize all stimuli (128 stimuli), whereas six NT participants reported having clearly identified the category C255 to be memorized (only eight stimuli).

Noteworthy, there were positive correlations between accuracy with the INT style and the perceptual reasoning score (IQ-PR), and between accuracy with the LUT style and the working memory score (IQ-WM) within the NT group, but not within the ASD group. This

suggests that, in the NT group at least, the participants' abilities to find the orientation rule and to perform 3D visual search were related, and so were their abilities to memorize the association between stimuli and answers and their working memory scores. However, in the ASD group, their IQ scores could not be related to the intra-group variability in making use of the LUT or INT style.

### ***Spontaneous versus instructed INT style***

We found that ASD participants were able to interpolate and categorize, but made less spontaneous use of this learning-style, as compared to NT. Hence, group differences to interpolate would be mostly explained by task instructions. It underlines the key role of task instructions which could explain the inconclusive results on categorization in ASD, and the need for highly structured and explicit rules or instructions for individuals with ASD.

Accordingly, in perceptual tasks, ASD individuals can show strong biases with implicit instructions but no differences with explicit instructions (Koldewyn et al. 2013; Van der Hallen et al. 2016). Indeed, the effect of the level of instructions was assessed in a study investigating global and local processing abilities in children with ASD in a free-choice task versus an instructed task (Koldewyn et al. 2013). This study revealed that children with ASD did not show a disability in global processing when they received explicit instructions, but showed disinclination in global processing in absence of explicit instructions. Likewise, a recent study involving visual search tasks showed that ASD children did not differ from typically developing children when given explicit instructions, but had a lower accuracy when they were less aware of the targets to search for (Van der Hallen et al. 2016).

The influence of task instructions could contribute to explain the inconsistent results on local and global processing in ASD, and the results from a recent meta-analysis showing no enhanced local processing, nor reduced global processing in ASD (Van der Hallen et al. 2015). Besides, in tasks assessing social cognition or executive functions, explicit instructions can also significantly reduce the impairment found in non-instructed conditions in ASD (Baez et al. 2012; Baez and Ibanez 2014; Senju et al. 2009; White et al. 2009). This difference was explained by difficulties to spontaneously integrate social and/or contextual information in ASD (Baez et al. 2012; Senju et al. 2009).

### ***Precision tuning in the learning-style theory***

The reduced automatic use of the INT style could be interpreted as a different precision tuning of the encoding of the training examples. In complex tasks involving several



features, a broad precision tuning is optimal (INT style), whereas in easier tasks involving only one feature, a narrower precision tuning is optimal (Qian and Lipkin 2011). After receiving the instructions on the orientation rule, the ASD participants might have been able to categorize stimuli as they needed to encode only one feature. Accordingly, another study showed that when ASD and NT participants were attending to the same features of a stimulus, people with ASD had similar performance as NT (Bott et al. 2006). Other visual tasks have investigated perceptual abilities in ASD in contexts where one or several features needed to be encoded. For instance, people with ASD showed enhanced perceptual abilities to detect orientation in a simple grid, but impaired abilities to detect orientation when noise was added to the grid (Bertone et al. 2005). This suggests that, in ASD, visual processing at a low-level can be enhanced, but that it might be impaired at a higher-level. In our tasks, a lower-level could correspond to tasks with instructions (where only the orientation needs to be encoded), and a higher-level could correspond to the non-instructed tasks (where several features, including noise, need to be encoded).

The learning-style theory of ASD is consistent with an older theory: *the Adaptive Resonance Theory* (Grossberg 1999). This theory stated that categorizing can be described as a top-down effect, decreasing differences within a category and increasing differences between categories. This top-down effect could adapt the precision tuning, with a broad precision leading to decreased differences and tight precision to increased differences between categories. In ASD, there could be a decreased influence of top-down categorical knowledge on discrimination (Soulières et al. 2007), which could explain the reduced use of the INT learning-style in ASD, which was found in the present study.

### ***From the learning-style theory to computational accounts of ASD***

Recently, learning in ASD was approached within the Bayesian framework. In this framework, percepts emerge from a weighted combination of sensory information and prior belief (Friston 2003). Priors typically capture the main features of the previously encountered stimuli and can be adjusted throughout learning. They are context-dependent and play a key role in categorization, generalization and prediction. The INT learning-style would allow broad priors. In contrast, the LUT learning-style favors the encoding of details and prevents from identifying commonalities between examples, which could be referred to as a set of precise priors.

Computational approaches have recently enabled to shed light on how people with ASD cope with different types of uncertainty, namely sensory ambiguity, probabilistic

uncertainty and environmental uncertainty (Lawson et al. 2017; Palmer et al. 2017). These three dimensions of uncertainty can be identified in our tasks. First, sensory uncertainty was manipulated as stimulus orientations were following a normal distribution. Yet, we did not find any impact of such a sensory noise on the difference in performance between groups. Second, probabilistic uncertainty was null, since each stimulus was surely predicting the correct response. What remained to be determined by the subject was the actual predicting rule at play. Finally, environmental uncertainty was introduced between blocks by changing the learning strategy, and within the Mixed LUT-INT task by mixing the type of stimulus-response association. We did observe a difference between groups in dealing with this environmental uncertainty, in the sense that only NT participants reported raising their strategy to the use of two rules in the case of the Mixed LUT-INT task. However, this may highlight another difference between ASD and NT participants than the one reported in Lawson et al. (2017). Indeed, while Lawson and colleagues studied associative learning, we investigated both the learning of a simple (deterministic) association and the ability to discover the predicting feature in the cueing stimulus.

This aspect and the finding that ASD participants proved impaired compared to NT will have to be further investigated. This should be studied from a computational perspective, in order to possibly identify common mechanisms that would also explain findings by Lawson et al. (2017), as well as findings about perceptual learning in probabilistic environments (Robic et al. 2014).

### ***Conclusion***

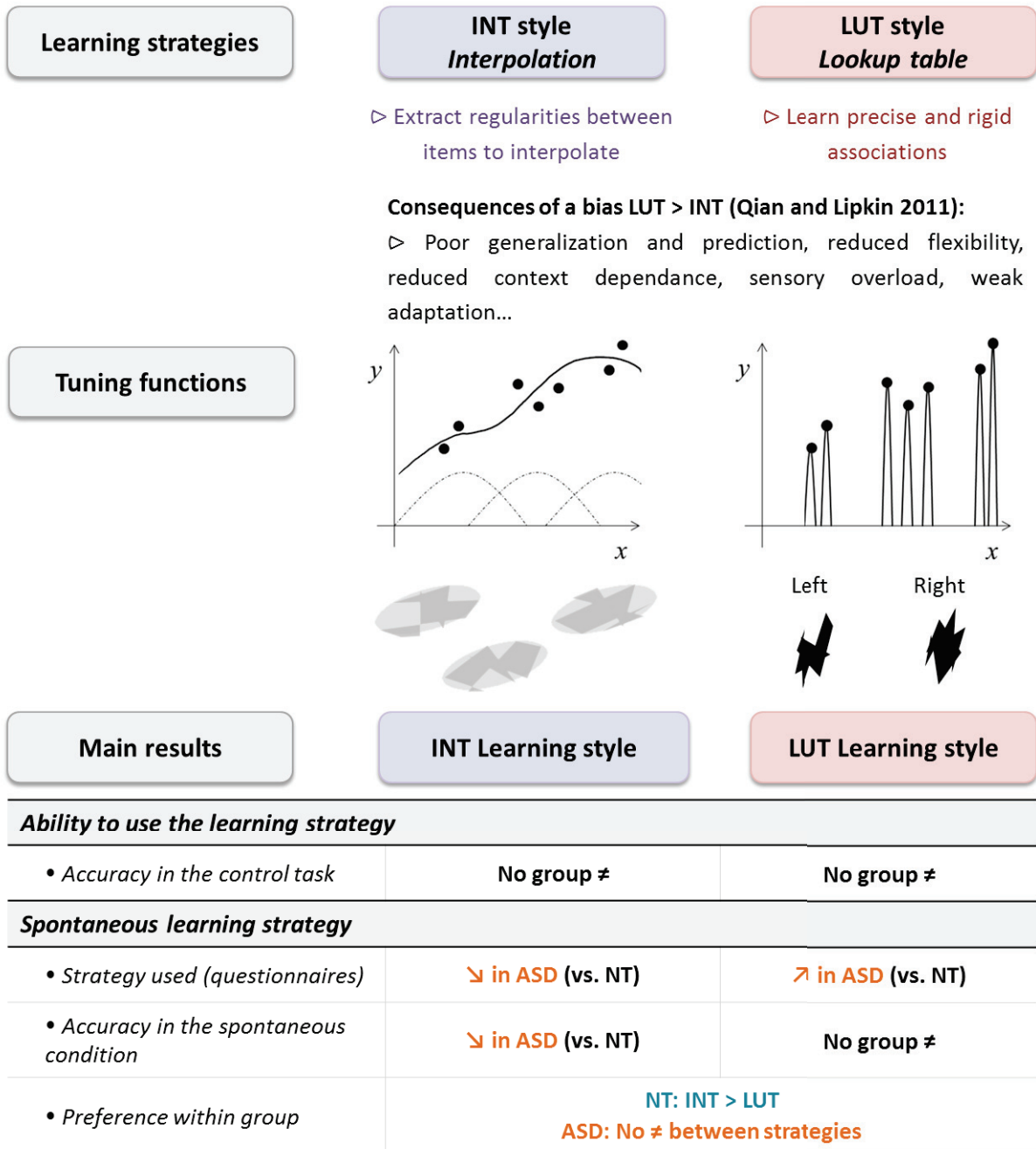
We showed that people with ASD were less inclined to search for global underlying regularities, despite intact abilities to categorize. A reduced automatic and implicit learning of these regularities might impact daily life, and particularly, the understanding of social interactions (e.g., recognizing facial expressions requires being able to interpolate between facial expressions previously encountered). Studying the learning-styles in ASD can have concrete applications on learning strategies to use with children with ASD, and could explain, for instance, their difficulties to catch grammatical regularities and extract rules in general. Further studies investigating the spontaneous use of LUT and INT strategies in children with ASD may shed light on how these specificities unfold during the development.

## References

- Alderson-Day, B., & McGonigle-Chalmers, M. (2011). Is it a bird? Is it a plane? category use in problem-solving in children with autism spectrum disorders. *Journal of autism and developmental disorders*, 41(5), 555–565. doi:10.1007/s10803-010-1077-9
- Asperger, H. (1944). Die ‘Autistischen Psychopathen’ im Kindesalter. *Archiv für Psychiatrie und Nervenkrankheiten*, 117, 76–136.
- Baez, S., & Ibanez, A. (2014). The effects of context processing on social cognition impairments in adults with Asperger’s syndrome. *Frontiers in Neuroscience*, 8, 270. doi:10.3389/fnins.2014.00270
- Baez, S., Rattazzi, A., Gonzalez-Gadea, M. L., Torralva, T., Vigliacca, N. S., Decety, J., et al. (2012). Integrating intention and context: assessing social cognition in adults with Asperger syndrome. *Frontiers in Human Neuroscience*, 6, 302. doi:10.3389/fnhum.2012.00302
- Baron-Cohen, S., Wheelwright, S., Skinner, R., Martin, J., & Clublely, E. (2001). The autism-spectrum quotient (AQ): evidence from Asperger syndrome/high-functioning autism, males and females, scientists and mathematicians. *Journal of Autism and Developmental Disorders*, 31(1), 5–17.
- Bertone, A., Mottron, L., Jelenic, P., & Faubert, J. (2005). Enhanced and diminished visuo-spatial information processing in autism depends on stimulus complexity. *Brain: a journal of neurology*, 128(Pt 10), 2430–2441. doi:10.1093/brain/awh561
- Bott, L., Brock, J., Brockdorff, N., Boucher, J., & Lamberts, K. (2006). Perceptual similarity in autism. *Quarterly journal of experimental psychology* (2006), 59(7), 1237–1254. doi:10.1080/02724980543000196
- Carmo, J. C., Souza, C., Gonçalves, F., Pinho, S., Filipe, C. N., & Lachmann, T. (2017). Effects of categorical representation on visuospatial working memory in autism spectrum disorder. *Journal of Clinical and Experimental Neuropsychology*, 39(2), 131–141. doi:10.1080/13803395.2016.1207754
- Church, B. A., Krauss, M. S., Lopata, C., Toomey, J. A., Thomeer, M. L., Coutinho, M. V., et al. (2010). Atypical Categorization in Children with High Functioning Autism Spectrum Disorder. *Psychonomic bulletin & review*, 17(6), 862–868. doi:10.3758/PBR.17.6.862
- Church, B. A., Rice, C. L., Dovgopoly, A., Lopata, C. J., Thomeer, M. L., Nelson, A., & Mercado, E. (2015). Learning, plasticity, and atypical generalization in children with autism. *Psychonomic Bulletin & Review*, 22(5), 1342–1348. doi:10.3758/s13423-014-0797-9
- Dawson, M., & Mottron, L. (2008). Learning in autism. In *Learning and Memory: A Comprehensive Reference III Cognitive Psychology* (J. Byrne and H. L. Roediger (Oxford: Elsevier).), pp. 759–772.
- Dawson, Michelle, Mottron, Laurent, & Gernsbacher, Morton Ann. (2005). Learning in Autism, Vol. [2] of *Learning and Memory: A Comprehensive Reference*, [759-772].
- Fisher, A. V., Godwin, K. E., Matlen, B. J., & Unger, L. (2014). Development of Category-Based Induction and Semantic Knowledge. *Child Development*. doi:10.1111/cdev.12277
- Friston, K. (2003). Learning and inference in the brain. *Neural networks: the official journal of the International Neural Network Society*, 16(9), 1325–1352. doi:10.1016/j.neunet.2003.06.005
- Frith, U. (1991). *Autism and Asperger Syndrome*. Cambridge University Press.
- Froehlich, A. L., Anderson, J. S., Bigler, E. D., Miller, J. S., Lange, N. T., DuBray, M. B., et al. (2012). Intact prototype formation but impaired generalization in autism. *Research in Autism Spectrum Disorders*, 6(2), 921–930. doi:10.1016/j.rasd.2011.12.006
- Gastgeb, H. Z., Dundas, E. M., Minshew, N. J., & Strauss, M. S. (2012). Category formation in autism: can individuals with autism form categories and prototypes of dot patterns? *Journal of autism and developmental disorders*, 42(8), 1694–1704. doi:10.1007/s10803-011-1411-x
- Gastgeb, H. Z., Rump, K. M., Best, C. A., Minshew, N. J., & Strauss, M. S. (2009). Prototype formation in autism: can individuals with autism abstract facial prototypes? *Autism Research: Official Journal of the International Society for Autism Research*, 2(5), 279–284. doi:10.1002/aur.93
- Gastgeb, H. Z., & Strauss, M. S. (2012). Categorization in ASD: The Role of Typicality and Development. *Perspectives on language learning and education*, 19(2), 66–74. doi:10.1044/ll19.2.66
- Grandin, T. (1997). A personal perspective on autism. In *Handbook of Autism and Pervasive Developmental Disorders* (Cohen, D.J. and Volkmar, F.R., eds) (pp. 1032–1042).

- Grossberg, S. (1999). The link between brain learning, attention, and consciousness. *Consciousness and Cognition*, 8(1), 1–44. doi:10.1006/ccog.1998.0372
- Kanner, L. (1943). Autistic disturbances of affective contact., *Nervous Child*, 2, 3, 217–250.
- Klinger, L. G., & Dawson, G. (2001). Prototype formation in autism. *Development and psychopathology*, 13(1), 111–124.
- Koldewyn, K., Jiang, Y. V., Weigelt, S., & Kanwisher, N. (2013). Global/local processing in autism: not a disability, but a disinclination. *Journal of Autism and Developmental Disorders*, 43(10), 2329–2340. doi:10.1007/s10803-013-1777-z
- Lawson, R. P., Mathys, C., & Rees, G. (2017). Adults with autism overestimate the volatility of the sensory environment. *Nature Neuroscience*. doi:10.1038/nn.4615
- Marcus, G. F., Fernandes, K. J., & Johnson, S. P. (2007). Infant rule learning facilitated by speech. *Psychological Science*, 18(5), 387–391. doi:10.1111/j.1467-9280.2007.01910.x
- Palmer, C. J., Lawson, R. P., & Hohwy, J. (2017). Bayesian Approaches to Autism: Towards Volatility, Action, and Behavior. *Psychological Bulletin*. doi:10.1037/bul0000097
- Plaisted, K. C. (2001). Reduced generalization in autism: An alternative to weak central coherence. In J. A. Burack, T. Charman, N. Yirmiya, & P. R. Zelazo (Eds.), *The development of autism: Perspectives from theory and research* (pp. 149–169). Mahwah, NJ, US: Lawrence Erlbaum Associates Publishers.
- Qian, N., & Lipkin, R. M. (2011). A learning-style theory for understanding autistic behaviors. *Frontiers in Human Neuroscience*, 5, 77. doi:10.3389/fnhum.2011.00077
- Robic, S., Sonié, S., Fonlupt, P., Henaff, M.-A., Touil, N., Coricelli, G., et al. (2014). Decision-Making in a Changing World: A Study in Autism Spectrum Disorders. *Journal of Autism and Developmental Disorders*. doi:10.1007/s10803-014-2311-7
- Scherf, K. S., Behrmann, M., Minshew, N., & Luna, B. (2008). Atypical development of face and greeble recognition in autism. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, 49(8), 838–847. doi:10.1111/j.1469-7610.2008.01903.x
- Senju, A., Southgate, V., White, S., & Frith, U. (2009). Mindblind eyes: an absence of spontaneous theory of mind in Asperger syndrome. *Science (New York, N.Y.)*, 325(5942), 883–885. doi:10.1126/science.1176170
- Soulières, I., Mottron, L., Giguère, G., & Laroche, S. (2011). Category induction in autism: slower, perhaps different, but certainly possible. *Quarterly journal of experimental psychology* (2006), 64(2), 311–327. doi:10.1080/17470218.2010.492994
- Soulières, I., Mottron, L., Saumier, D., & Laroche, S. (2007). Atypical Categorical Perception in Autism: Autonomy of Discrimination? *Journal of Autism and Developmental Disorders*, 37(3), 481–490. doi:10.1007/s10803-006-0172-4
- Van der Hallen, R., Evers, K., Boets, B., Steyaert, J., Noens, I., & Wagemans, J. (2016). Visual Search in ASD: Instructed Versus Spontaneous Local and Global Processing. *Journal of Autism and Developmental Disorders*, 46(9), 3023–3036. doi:10.1007/s10803-016-2826-1
- Van der Hallen, R., Evers, K., Brewaeys, K., Van den Noortgate, W., & Wagemans, J. (2015). Global processing takes time: A meta-analysis on local-global visual processing in ASD. *Psychological Bulletin*, 141(3), 549–573. doi:10.1037/bul0000004
- Vladusich, T., Olu-Lafe, O., Kim, D.-S., Tager-Flusberg, H., & Grossberg, S. (2010). Prototypical category learning in high-functioning autism. *Autism research: official journal of the International Society for Autism Research*, 3(5), 226–236. doi:10.1002/aur.148
- Weston, D. R., & Turiel, E. (1980). Act–rule relations: Children’s concepts of social rules. *Developmental Psychology*, 16(5), 417–424. doi:10.1037/0012-1649.16.5.417
- White, S. J., Burgess, P. W., & Hill, E. L. (2009). Impairments on “open-ended” executive function tests in autism. *Autism Research: Official Journal of the International Society for Autism Research*, 2(3), 138–147. doi:10.1002/aur.78

## Synthesis



Remarkably, in ASD, the decreased use of the INT learning strategy did not seem to be due to visual hypersensitivity, as there was no correlation between the tendency to use the this learning strategy and hyper or hypo-sensitivity trait, measured by the GSQ. Some other deeper perceptual or learning processes might have contributed to the decreased tendency to interpolate between stimuli to build up high-level priors.

### III. Study III: Atypical perceptual learning in ASD

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#### *Preamble*

*« Their world must seem to them to be made of elements that, once they have been experienced in a certain setting or sequence, cannot be tolerated without all the original ingredients in the identical spatial or chronological order. »*

*Kanner, 1943*

*« Once I have built up a clear image about what to do, or what is going to happen next, and that somebody changes the program, it devastates me, and I need time to try to get adapted to it. »*

*Participant with ASD (I.S.)*

*« His own face in the mirror, his own hands, surprised him on every occasion... He was the solitary and lucid spectator of a multiform world which was instantaneously and almost intolerably exact... He was not very capable of thought. To think is to forget a difference, to generalize, to abstract. »*

*Borges 1942 (cited in Van de Cruys et al. 2014)*

According to the Bayesian view of perception, our brain constantly builds and adjusts some internal representations of the world. The above testimonies suggest that autistic people do so but suffer from the frequent violations of the expectations that result from those representations. People with ASD often report that they are frequently surprised, and that is an important source of anxiety. Surprises reflect a mismatch between the true sensations and the expected ones. Interestingly, in a very inspiring first attempt to a Bayesian account of ASD core symptoms, it was suggested that individuals with ASD would entertain very unprecise priors, therefore not influencing much their perception (Pellicano and Burr 2012). Following this article by Pellicano and Burr, it was underlined that a perception not biased toward priors could also be due to too precise sensory information (Brock 2012). Afterwards, Lawson and colleagues highlighted the importance of precision or confidence in tuning the relative influence of sensory information and priors (Lawson et al. 2014). In ASD, an imbalance between those precisions, in favor of bottom-up signals, would yield too highly weighted prediction errors, even though contextual information would be available to reduce prediction error. As thoroughly demonstrated and discussed by several review papers, this core computational mechanism may explain many of the core symptoms in ASD. Interestingly, it may bridge the gap between social and non-social symptoms. It also gives the opportunity to use simple tasks pertaining to non-social stimuli to shed light on those mechanisms. As the

usefulness of these computational approaches is being recognized, they now need to unfold in quantitative models to enable the fine characterization of ASD. A characterization that may yield to refined diagnosis and therapies but which should also explain on the way the apparent contradistinction between the many empirical studies in the literature that can be revisited to test this new theory.

Here, we wanted to contribute to this important and fairly young endeavor. We decided to design a simple perceptual decision task that would enable us to start refining the mechanisms at play in the peculiar perception of ASD people. The aims of the following study was (1) to determine whether individuals with ASD were able to implicitly learn priors in the first place and if so, (2) to assess how priors would weight perception and how this weight would be modulated by the experimental context, (3) to investigate the dynamics of implicit learning following changes in the environment.

In this aim, we used a tactile discrimination task designed to elicit a time-order effect (TOE). Participants simply had to compare the frequencies of two tactile stimulations, successively delivered on their finger. As detailed in the theoretical background (II.1.C), the TOE reflects how prior knowledge influences perceptual decisions. Eliciting a TOE is thus an efficient way of testing the implicit learning of contextual regularities. A TOE is elicited in contexts where sensory stimuli are ambiguous enough, so that prior significantly contribute to the perceptual decisions. In our task, the prior pertains to the frequency of the stimulations to come. In particular, a reduced influence of the priors in ASD would result in the absence or reduction of the TOE. Furthermore, the impaired learning or inflexible adjustment of prior beliefs would be reflected by a lack of modulation of the TOE by the experimental context. And importantly, these impairments can readily be interpreted in terms of inflexible adjustments of learning rates or precision weights applied to prediction errors.

We tested these predictions in a behavioural study experiments made of two experiments: a first time-order task in a (more) stable perceptual context, and a second time-order task in a (more) volatile perceptual context. Given the testimonies of subjects with ASD, we could hypothesize that in (very) stable contexts, they would be able to build up (strong) priors but would show difficulties in adjusting them. Indeed, patient I.S. mentioned that once she has a clear and strong prediction, she can adjust it, but it takes her longer than to NT subjects. To precisely characterize perceptual inference in NT and ASD groups, we used a computational model of observed behavior. This model provides estimates of sensory precision and of the nature and weight of prior beliefs.

## ***Article***

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### **Behavioral evidence for a maladaptive perceptual inference in autism**

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#### ***Abstract***

Bayesian theories were formulated to explain the computational and neurophysiological counterparts of atypical perception in Autism Spectrum Disorders (ASD). In this framework, perception is influenced by both the estimated precision of sensory inputs and our expectations (*priors*). ASD has been suggested to be characterized by an imbalance in the way *prior* information and sensory evidence are traded. However, evidence in favor of this hypothesis remains scarce.

In order to test and refine this hypothesis, we studied implicit *prior* learning and adjustment in ASD. Neutotypicals (NT) and ASD adults performed adaptation measurements, as well as two tactile frequency discrimination tasks designed to elicit the so-called time-order effect (TOE), whereby the percept of the first stimulus appears to be strongly biased in an ambiguous context. We developed a computational model to quantify the relative weights of prior belief and sensory information onto perceptual decisions, respectively.

Both ASD and NT subjects showed a TOE, revealing the construction of *priors* and their influence on perception. However, ASD participants did not flexibly modulate the weight of *prior* on perception, be it in a more stable or more varying perceptual context, as opposed to NT. Finally, the ASD group showed no adaptation effect contrary to NT.

These results show that people with ASD can implicitly build and adjust priors, but with a slower dynamic than NT. This atypical perceptual inference in ASD fits with well-known higher level symptoms, such as resistance to change and inflexibility.

***Keywords:*** autism, Bayesian, perceptual learning, tactile discrimination, time-order effect



## *Introduction*

Facing a changing environment, our brain perpetually updates internal representations or expectations pertaining to upcoming sensations. In Bayesian terms, priors correspond to these internal references, dynamically adjusted through implicit or explicit learning. Weighted priors beliefs will be combined with weighted sensory information to generate percepts or posteriors. Importantly, those weights reflect the inferred precision or confidence attached to priors and sensations. A tight prior corresponds to a high confidence in predicting sensory inputs, while a very informative sensory input will be affected a high precision. In ambiguous environments where sensations are noisy, perception is particularly biased toward priors since low confidence must be attributed to sensory inputs. Bayesian computation will optimally combine those two weighted sources of information, and yield an optimal percept, provided that the relative precisions have been accurately estimated. The discrepancy between priors and sensory evidence generate precision weighted prediction errors. Prediction errors are given a low precision when they signal noise or irrelevant variability. Conversely, they are given a high precision for relevant information and will drive the updating of current beliefs to shape future expectations.

Recently, Bayesian theories of Autism Spectrum Disorders (ASD) were formulated to explain how the perception of the world could be altered in ASD (Friston 2003; Brock 2012; Pellicano and Burr 2012; Friston et al. 2013; Lawson et al. 2014; Sinha et al. 2014; Van de Cruys et al. 2014; Friston 2016). Together with computational modeling, these theories can help disentangling the complex spectrum aspect of neuropsychiatric diseases such as ASD (Stephan et al. 2015; Huys et al. 2016). ASD is characterized by behavioral impairments in social interactions, repetitive and restricted interests, as well as peculiarities of perception (American Psychiatric Association 2013). The core mechanisms at the origin of social and non-social autistic symptoms could be characterized within the Bayesian framework (Van de Cruys et al. 2014; Friston 2016; Haker et al. 2016). Indeed, an ongoing and thought provoking theoretical debate intends to explain behavioral impairments such as those encountered in ASD, as the expression of altered probabilistic inference and learning (Brock 2012; Pellicano and Burr 2012; Friston et al. 2013; Lawson et al. 2014; Van de Cruys et al. 2014). It has been first suggested that people with ASD might have a perception “closer to reality” than neurotypicals (NT) (Pellicano and Burr 2012). Precisely, impaired adaptation of prior precision would prevent them from making suitable predictions and would typically yield an aversive and protective behavior towards (unexpected) changes in the environment, leading to

flexibility issues (Gomot and Wicker 2012; D’Cruz et al. 2013; Robic et al. 2014). An inappropriate construction of priors would explain the failures in building up rules essential to generalize and categorize, as encountered in ASD (Church et al. 2010; Froehlich et al. 2012). An increased weighting of sensory inputs could be linked with low endogenous neural noise (Davis and Plaisted-Grant 2015), hypersensitivity and acute discrimination abilities in ASD (Mottron et al. 1999, 2006).

Three main mechanistic hypotheses of atypical weighting of priors and sensory inputs in ASD were formulated. First, the hypo-prior hypothesis suggests that priors are too blurred in ASD, so that they poorly influence perception (Pellicano and Burr 2012), consistently with the idea that people with ASD would be less influenced by prior in perceptual tasks (Ropar and Mitchell 2002). Second, the high sensory accuracy hypothesis suggests that sensory information could be afforded a too high precision when computing the percept (Brock 2012; Lawson et al. 2014). This could explain that individuals with ASD are less susceptible to visual illusions than NT (Happé 1996; Mitchell et al. 2010). The third hypothesis supposes a high inflexible precision of prediction error in autism (HIPPEA) (Van de Cruys et al. 2014). Rather than considering the precision of priors or sensory inputs independently, it is crucial to consider a precision balance. A defect in attributing accurate precisions, for instance, if sensory information is not contextualized, would give rise to too precise and context-insensitive prediction errors (Lawson et al. 2014). It would also lead to unsuitable predictions since noisy sensory inputs would be erroneously considered as relevant and would systematically challenge the existing priors. HIPPEA is consistent with peculiarities of flexibility, sensibility, attention, executive functions, perception and social cognition encountered in ASD (Van de Cruys et al. 2014).

As recently reviewed (Haker et al. 2016), current evidence supporting these computational hypotheses in ASD remain scarce. Recent studies investigating prior influence on perception in ASD suggested intact priors in subjects with high autistic traits (Ewbank et al. 2016) and with ASD (Corbett et al. 2016; Ego et al. 2016; Pell et al. 2016). Yet, Karaminis et al. (Karaminis et al. 2016) found greater prior influence in a temporal domain in ASD, but interpreted that the use of priors did not increase enough in ASD children to compensate for their poor temporal resolution, and concluded toward the hypo-prior hypothesis. Note that this study only relies on temporality of motor responses and assumes no impaired motor abilities in children with ASD, despite existing impairments (Schmitz et al. 2003; Green et al. 2009; Fournier et al. 2010; Gowen and Hamilton 2013; Biscaldi et al. 2014). Evaluating the bases of Bayesian theories in ASD requires subtle tools where the precision balance and the dynamic

adjustment of the precision of the prediction error and prior need to be carefully studied (Van de Cruys et al. 2013).

The present study aims at understanding prior construction and adjustment in ASD, in order to determine whether one of the above hypotheses prevail in ASD. It uses a simple and well-established tactile discrimination task. Participants performed a frequency discrimination task based on tactile modality to minimize chances of having strong expectations regarding the stimulations, or of having elaborated compensation strategy throughout development. In order to assess how ASD and NT subjects were influenced by contexts, we made use of the so-called time-order effect (TOE). This robust and well-documented effect relates to the central tendency of judgement (Hollingworth 1910; Sinclair and Burton 1996; Romo et al. 2000; Harris et al. 2006; Preuschhof et al. 2010; Ashourian and Loewenstein 2011; Karim et al. 2013). A contraction bias emerges in sequential judgments of similar stimuli along a particular dimension (e.g. frequency), where stimulations seem closer to the prior (e.g. mean frequency) than they really are. It leads to overestimation of stimuli lying in the lower range of stimulations, and underestimation of those lying in the upper range. The TOE is subsequent to this bias and can be observed in two-alternative forced choice tasks, where the strength of the contraction bias differs between the two stimulations. In ambiguous contexts, the percept of the first stimulus is more biased toward priors, since it has to be stored in memory during the delay period (Ashourian and Loewenstein 2011). Importantly, it is in uncertain environments that the most pervasive difficulties of ASD should emerge (Lawson et al. 2014). TOE tasks can highlight prior learning and relative weighting of precision depending on contexts.

Van de Cruys et al. (2013) predicted that high sensory precision at the early stages of sensory processing would lead to upregulated prediction errors, inducing narrow priors that would be hardly adapted in changing contexts. Following these hypotheses, several subtle predictions can be made on prior construction and adaptation in ASD in our perceptual task. First, we assume that a long lasting exposure to a stable experimental context would enable ASD subjects to build up a precise and strongly influencing prior. Hence, the TOE should not only be visible but even stronger in ASD subjects compared to NT. Second, in a varying environment, their more inflexible mind would reveal a maladaptive behavior. In other words, when suddenly changing the frequency range, the TOE should be adjusted to the new range slower in ASD than NT subjects, or not adjusted at all. Third, we assume that precision of prediction errors would be inflexible in ASD. Therefore, contrary to NT, the relative weight of prior on perception should not be modulated by the instability of the context in the ASD

group. We tested these predictions in Experiments 1 and 2 and used a simple computational model of the TOE to further emphasize the relationship between weighted prediction errors and the observed behavior. Finally, we measured tactile adaptation in the short experiment 0. As adaptation reflects the adjustment of sensory systems according to prior experience, which can be seen as the flexible suppression of prediction errors for predictable stimuli (Summerfield et al. 2008; Lawson et al. 2014), we expect adaptation to be reduced in the ASD group as compared to NT.

## *Material and Methods*

### *Participants*

All participants were adults aged between 18 and 60 years. ASD subjects were diagnosed by a psychiatrist specialized in autism, according to the Diagnostic and Statistical Manual of Mental Disorders V (American Psychiatric Association 2013), and to their scores at the ADI-R (Autism Diagnostic Interview-Revised (Lord et al. 1994)), and/or the ADOS-G (Autism Diagnosis Observation Schedule (Lord et al. 1989)), or the AAA (Adult Asperger Assessment (Baron-Cohen et al. 2005)). ASD subjects presented with no language onset delay or intellectual deficiency. All subjects had no history of neurological disorders, and none of the NT subjects had history of psychiatric disorder. Every participant completed the Autism Quotient (AQ) questionnaire (Baron-Cohen et al. 2001) and the Glasgow Sensory Questionnaire (GSQ (Robertson and Simmons 2013)). Participants gave their written informed consent beforehand. Approval was obtained from the local ethics committee (South East IV Committee for the Protection of Persons).

Here follows the description of the ASD and NT groups of subjects who participated to each experiment. Some participants were involved in the three experiments (2 NT and 12 ASD), but their participations to experiments 1 and 2 were separated by a minimum of 10 months.

#### *Experiment 0: Tactile detection*

Thirty-five NT subjects (8 females) and 28 subjects with ASD (8 females) were involved in Experiment 0. The two groups were matched for age (NT:  $37 \pm 10$ , ASD:  $33 \pm 9$ ).

#### *Experiment 1: Time-order effect in a stable context*

Seventeen NT subjects (5 females) and 16 subjects with ASD (4 females) were involved in this experiment. The two groups were matched in age (NT:  $30 \pm 9$ , ASD:  $33 \pm 9$ )

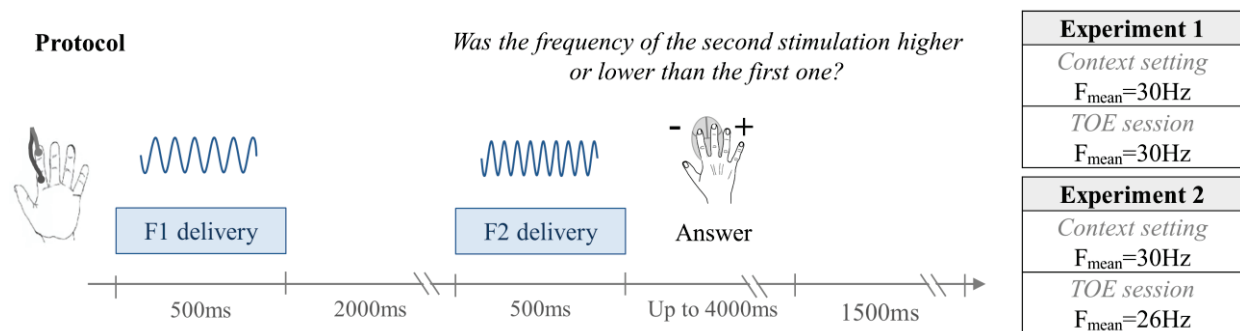
and education level, defined as the number of years of study after A-level (NT:  $4 \pm 2$ , ASD:  $4 \pm 3$ ). The NT group scored 12 ( $\pm 5$ ) at the AQ and 44 ( $\pm 15$ ) at the GSQ, while the ASD group scored 37 ( $\pm 7$ ) at the AQ and 76 ( $\pm 31$ ) at the GSQ.

### *Experiment 2: Time-order effect in a changing context*

Twenty NT adults (six females) and 17 adults (five females) with ASD were enrolled in this second study. The two groups were matched in age (NT:  $35 \pm 13$ , ASD:  $34 \pm 10$ ) and education level (NT:  $3 \pm 2$ , ASD:  $4 \pm 2$ ). The mean score at the AQ and GSQ were respectively 12 ( $\pm 4$ ) and 41 ( $\pm 14$ ) in the NT group, and 34 ( $\pm 9$ ) and 72 ( $\pm 28$ ) in the ASD group.

### **Tactile stimulations**

Two gold electrodes were taped on the first and third phalanx of the left index finger of each subject. Electrical stimulations were delivered by a constant current stimulator (GRASS technology). The electrical stimulation was felt on the internal face of the third phalanx (cathode electrode). Stimulations were composed of 5ms-long boxcar pulses, repeated at a given frequency. The overall tactile stimulation lasted 500ms.



### **Figure 1: Experimental design**

**A.** Tactile perceptual threshold measurement: subjects had to indicate as soon as they detected the stimulation (De: detection) and when they could not feel it anymore (Di: disappearance). This procedure was done twice.

**B.** At each trial, subjects received two successive non-painful electrical finger stimulations whose frequencies had to be compared. F1: 1<sup>st</sup> stimulation at frequency F1, F2: 2<sup>nd</sup> stimulation at frequency F2.

### **Tactile detection threshold**

The tactile detection threshold was estimated in each subject, prior to each experiment and following a classical staircase procedure (Fig. 1.A) (47). The aim was twofold: (i) matching the subjective stimulation intensity between subjects for the subsequent discrimination task; (ii) comparing NT and ASD subjects in terms of both the mean and the variance of this threshold. The intensity of the electrical stimulation was gradually increased

and then decreased. Each subject was asked to report when the tactile sensation started to be perceived (during the increase of stimulus intensity) as well as when the sensation disappeared (during the decrease). Starting from 0mA, the stimulus intensity was increased by 0.02mA every second. Subjects were told to raise their non-stimulated hand or to give an oral indication, as soon as they could feel the stimulation and this first detection threshold value was collected. We kept on increasing the intensity until reaching 1.5 times this threshold value. Then, we used the same progression to decrease the intensity and subjects had to lower their non-stimulated hand or to give an oral indication as soon as the sensation would disappear. This procedure was repeated twice, resulting in four measures of threshold: two of detection and two of disappearance.

#### ***Adaptation assessment (Experiment 0)***

Adaptation is a process which “*reduces redundancy by biasing perception away from repeated features in the environment, making novel stimuli and features more salient*” (48). The threshold measurement procedure involves a prolonged exposure to tactile stimulations, and might thus be significantly influenced by adaptation (49). If so, detection of a change should be biased differently, depending on whether the stimulus intensity is being increased or decreased. Precisely, detection of the stimulation should occur at a lower intensity than the feeling of its disappearance. We assessed the adaptation effect (AE) by computing, in each subject, the averaged difference between the disappearance and detection intensities. We tested whether AE was significantly greater than zero in each group, and compared AE values in the two groups.

#### ***Tactile discrimination (Experiments 1 and 2)***

The intensity of the electrical stimulations aimed to be at 2.5 times their detection threshold (50). Yet, for some of the NT subjects, and more specifically for the ASD subjects, we allowed a slight reduction of this factor in order to guarantee to maintain a comfortable (non-painful and non-itchy) but clearly perceived stimulus. This ended up with similar multiplying factors between the two groups: 2.4 in the NT group and 2.2 in the ASD group. The intensity was kept constant during the whole task.

At each trial, subjects received two successive stimulations to be compared in frequency (Fig. 1.B). Each stimulation lasted 500ms, and the time interval between the two stimulations was fixed and equal to 2000ms. A white fixation cross was displayed on the center of the computer screen during stimulations and delay. Right after the delivery of the second stimulation, a question mark appeared on screen to indicate that an answer was

expected. Subjects had up to 4 seconds to answer by clicking on the computer mouse buttons, using their dominant hand. If the second stimulation was perceived as higher in frequency than the first one, they had to click on the side of the *plus* sign (+), as shown on screen. Conversely, if it was perceived as lower, they had to click on the side of the *minus* sign (-). Finally, a black screen appeared after the mouse click and the next trial would start after a fixed inter-trial interval of 1500ms. The sides corresponding to the *plus* (+) and *minus* (-) answers respectively, were indicated on screen at each trial and never changed for a given subject but were counterbalanced over subjects. No feedback was provided.

The experiment was programmed using the software package Presentation (Neurobehavioral Systems). Subjects were told to prioritize accuracy over speed. The whole experiment consisted of 447 trials, and each trial lasted for 5.3sec on average. It was divided into five blocks (7 to 8 minutes each), separated by 2-minute breaks. Subjects began the task after having completed a 16-trial long training made of one sample of each possible pair of stimuli that would be presented during the context setting trial blocks.

- ***Blocks n°1, 2, 3: Context setting*** (same design in experiments 1 and 2)

These initial blocks aimed at familiarizing the subjects with the task and at inducing a context-based prior on the expected range of stimulus frequencies.

During these first three blocks, the frequency of the first stimulation (F1) was always the same and equal to 30Hz. The frequency of the second stimulation (F2) was 0 to 8Hz higher or lower than F1 (F2=22:38Hz). The 17 possible pairs of frequencies were repeated five times each per block. Each block thus consisted of 85 trials: 40 trials in which F2 was higher than F1, 40 trials where F2 was lower than F1 and 5 trials where F2 was equal to F1 (the latter were discarded from the analyses). By keeping the first stimulation constant, we induced a strong prior expectation of 30Hz stimulation for F1.

Subjects who got less than 56.5% of correct answers (chance level, according to binomial law for  $p=0.05$ ) during the context setting blocks were excluded from the analysis. The ASD subjects who were excluded could not perform the task because of their hypersensitivity ( $n=4$ ), hyposensitivity due to damaged fingers ( $n=2$ ), their high fatigability ( $n=1$ ) or the disturbing sensation produced by the adhesive tape ( $n=1$ ). In total, 7 ASD subjects and one NT subject were excluded.

- ***Blocks n°4 and 5: Time-order effect***

These two blocks aimed at assessing the TOE. Subjects were not informed that the design of these two blocks was different from the one in the three preceding blocks. Each

block consisted of 96 trials with 8 presentations of each of the 12 new pairs of frequencies. Trials were pseudo-randomly ordered (successive trials were never identical). Importantly, to induce a TOE and regardless of the experiment, the frequency of F1 was no more constant but, within a trial, the absolute difference in frequency between the two stimulations was always equal to 2Hz.

In experiment 1, the frequency of the first stimulation could take six different values with equal probability (F1=25, 27, 29, 31, 33 or 35Hz). This frequency range is centered on 30Hz. The second stimulation was always 2Hz higher or lower than F1, with equal probability (F2=23, 25, 27, 29, 31, 33, 35 or 37Hz).

In experiment 2, the frequency of the first stimulation F1 could take six different values with equal probability (F1= 21, 23, 25, 27, 29 or 31Hz). This frequency range is centered on 26Hz. The second stimulation was always 2Hz higher or lower than F1, with equal probability (F2=19, 21, 23, 25, 27, 29, 31 or 33Hz).

### ***Time-order effect***

The time-order effect (TOE) is reflected by a biased perceptual decision, because of a context-based over-estimation or under-estimation of the first stimulus frequency. This bias has been shown to be expressed in both accuracy and reaction times (37). The TOE can be quantified as follows. For each possible value of F1, we compute the difference in accuracy between the case where F2 was 2Hz higher than F1 and the case where it was 2Hz lower (e.g. 25Hz-27Hz vs. 25Hz-23Hz). Averaged over all F1 values and divided by the individual mean accuracy, this yields what we refer to as the TOE index, denoted as  $I_{TOE}$ . Note that this index has no unit and is null in the absence of TOE.

### ***Perceptual decision model***

We introduce a simple probabilistic model of the TOE, based on very few and directly interpretable parameters that are sufficient to explain choices in the discrimination task and to test alternative computational hypotheses to explain the differences in behavior between ASD and NT subjects (see supplementary information for the full model derivation).

This model rests on a Bayesian account of the perception of the two stimuli, of the effect of maintaining the first frequency in working memory (at the origin of the TOE) and of the ensuing decision (40). The model emphasizes the role of three parameters: the prior mean or expected (log) frequency  $\theta_0$ ; the sensory precision  $\pi_\zeta$  and the TOE coefficient  $\gamma$ . The latter captures the amplitude of the TOE and writes:



$$\gamma = \frac{1 + r_1}{1 + r_2} - 1 \quad (1)$$

where  $r_i$  indicates the prior to sensory precision ratio pertaining to stimulation  $F_i$ . The TOE vanishes when  $\gamma$  equals zero. In contrast, there is a TOE ( $\gamma > 0$ ) as soon as the precision ratio for  $F_1$  is greater than the one for  $F_2$  (see SI-1 for more details). This direct dependency of the amplitude of the TOE upon precision ratios is crucial for testing an aberrant precision account of autism (5). This highlights how this task may help distinguishing between alternative processes of precision tuning to explain a behavioral difference between ASD and NT subjects.

In particular, if ASD subjects would entertain a higher sensory precision than NT subjects (3), the model predicts that they should obtain a higher discrimination accuracy (i.e. higher  $\pi_S$  in ASD), but no difference in their TOE (i.e. no group difference in  $\gamma$ ).

Conversely, according to the weak prior hypothesis (2), one would expect a similar accuracy (i.e. no group difference in  $\pi_S$ ) but a much weaker TOE in ASD compared to NT (i.e. lower  $\gamma$  in ASD).

Finally, if ASD subjects differ from NT in the way they adapt the relative precision of sensory inputs and priors to the given context, the above model should support such an explanation by showing no consistent difference among groups due to a systematic difference in accuracy or TOE, but rather a context-dependent difference. In particular, one would expect that ASD subjects adapt more slowly, which would yield a difference in parameter  $\theta_0$  after a contextual change, as well as a context-dependent difference in the parameter  $\gamma$  since the TOE is highly sensitive to this adjustment.

In practice, since parameter  $\theta_0$  could only take a limited number of possible values (within the range of delivered stimulations), we considered it a known model parameter and used Bayesian model comparison to estimate its most plausible value or range of values. This left us with two parameters to be estimated for each model,  $\pi_S$  and  $\gamma$ .

In Experiment 1 where both the context-setting and TOE blocks were centered on 30Hz, we set  $\theta_0$  to 30Hz.

In Experiment 2, where the TOE block was centered on 26Hz whereas the context-setting block was centered on 30Hz, we considered nine models. These models corresponded to  $\theta_0$  going from 22Hz up to 30Hz by steps of 1Hz. We fitted each model independently for each subject. Model fitting was performed on TOE blocks of Experiment 2 by either considering the two blocks (4 and 5) together or separately. We report the results of both a random-effect (RFX) model-family comparison and a fixed-effect (FFX) model comparison.

The two model families correspond to the low (between 22 and 26Hz) and the high prior mean frequencies (from 27 to 30Hz), respectively.

Finally, we fitted a simplified version of this model on the context setting blocks, with no time order effect and a prior mean frequency equal to 30Hz. This model has a single parameter  $\beta$ , as defined by the equation R3 (SI-1).

### ***Questionnaire***

Following the TOE experiments, subjects completed a questionnaire. They were asked to rate the difficulty of the task (in general, and per session). They also had to say whether they had had the feeling that the intensity of the stimulation varied across the tasks, whether the 1<sup>st</sup> or 2<sup>nd</sup> stimulation always remained at the same frequency (if so, at which block), and whether they thought they had answered “plus” or “minus” most frequently. They were free to add any comment, concerning the strategy used.

### ***Statistical analysis***

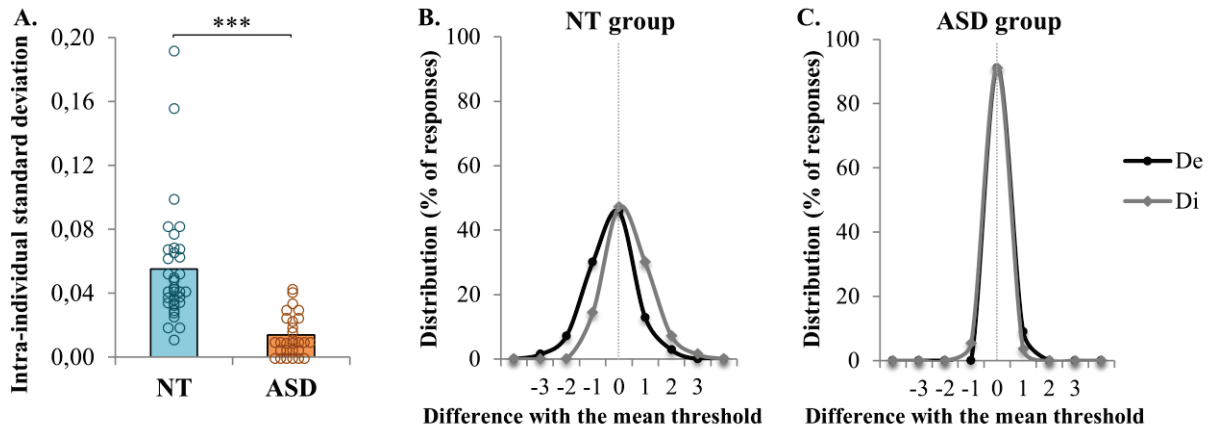
Demographic data and tactile detection thresholds were compared between groups using unpaired t-tests. Within group repeated measures ANOVAs were used to assess the accuracy and response times over the five blocks, in each of the two experiments, and Tukey’s tests were used post-hoc. TOE blocks were also analyzed with two-way nested ANOVAs, with the factor subject nested in the factor group and two main factors: group and TOE blocks. Correlations between the AQ or GSQ scores and task-related measures or inferred parameters were assessed using Pearson’s  $r$ . Unanswered trials were excluded from all the above analyses (they represent less than 0.01% of all recorded trials). All statistical analyses were performed using R (<http://www.r-project.org/>). The threshold for statistical significance was set to  $p < .05$ .

## ***Results***

### **Detection threshold variability measurement**

#### ***Mean detection threshold***

At 30Hz, the average detection threshold was not different between the NT (0.6mA  $\pm$ 0.2) and ASD (0.6mA  $\pm$ 0.4) groups. In the NT group only, this threshold was positively correlated with the total GSQ score of hyposensitivity ( $r = .54, p < .001$ ) and with the tactile GSQ score of hyposensitivity ( $r = .44, p < .01$ ).



**Figure 2: Experiment 0: tactile perception threshold in the NT and ASD groups**

**A.** Intra-individual standard deviation of the tactile perception threshold measurements. \*\*\*:  $p < 10^{-4}$

**B.** Distribution of the individual dispersion of the perception threshold, in the NT and ASD group, as an illustration of the adaptation effect. The x-axis presents the percentage of measures which differed by  $x$  mA from the mean threshold: unit -3:  $\leq -0.15$ mA, unit -2:  $[-0.15:-0.09]$ , unit -1:  $[-0.09:-0.03]$ , unit 0:  $[-0.03:0.03]$ , unit 1:  $[0.03:0.09]$ , unit 2:  $[0.09:0.15]$ , unit 3:  $\geq 0.15$ mA.

De: detection of a tactile sensation, Di: disappearance of the sensation.

### ***Intra-individual standard deviation and sensory adaptation***

The intra-individual standard deviation (iiSD) of the four threshold measures was higher in the NT group than in the ASD group (NT: 0.06, ASD: 0.01,  $p < 10^{-6}$ ) (Fig. 2.A).

We found an effect of sensory adaptation in the NT group (AE = 0.08,  $p < .01$ ), but not in the ASD group (AE = 0.01) (Fig. 2.B). AE was significantly higher in the NT than in the ASD group ( $p < .01$ ).

## **Experiment 1**

The tactile detection threshold did not differ between groups (0.5mA  $\pm$ 0.2 in both groups).

### ***Accuracy and reaction times***

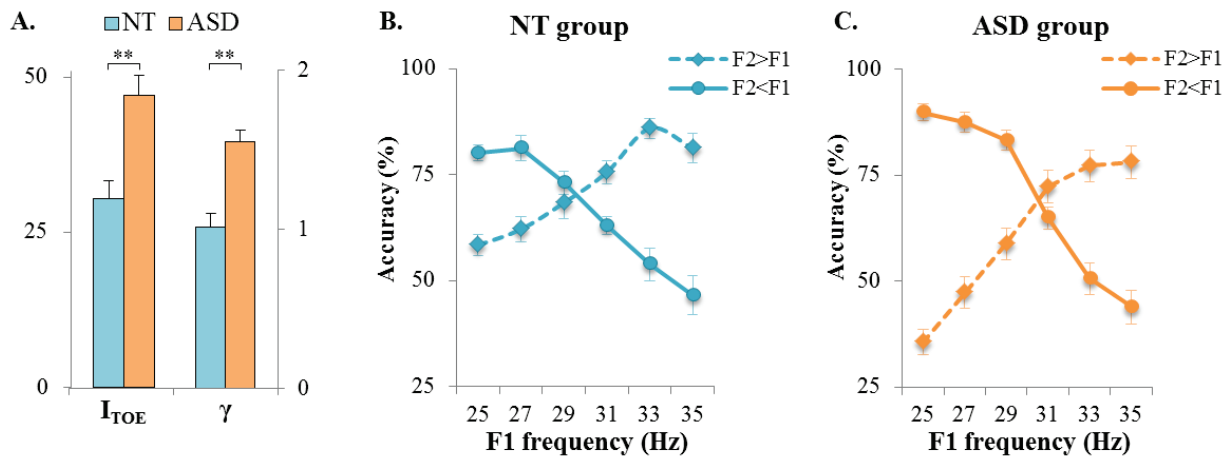
- *Context setting blocks (1 to 3)*

Accuracy did not differ between groups, with 81% ( $\pm$ 8) correct answers for the NT and 79% ( $\pm$ 7) for ASD subjects. The two groups answered as quickly on average (NT: 926ms  $\pm$ 432, ASD: 737ms  $\pm$ 252). There was no block effect on either accuracy or reaction times (RT), in both groups.

- *TOE blocks (4 and 5)*

No difference in accuracy was found between the two groups (NT: 69%  $\pm$ 8, ASD: 66%  $\pm$ 5). On average, ASD subjects answered faster than NT ones (ASD: 629ms  $\pm$ 206 vs.

NT:  $899\text{ms} \pm 449$ ,  $p < .05$ ). Contrary to the NT, the ASD group answered faster in the TOE blocks than in the context-setting blocks ( $628\text{ms} \pm 206$  vs.  $737\text{ms} \pm 252$ ,  $p < .02$ ).



**Figure 3: Experiment 1 – Time-order effect in a stable context**

**A.** Time-order index  $I_{TOE}$  and  $\gamma$  in TOE blocks in the NT (blue) and ASD (orange) groups.

**B-C:** Percentage of correct answers during the TOE blocks in the NT (B) and ASD (C) groups. “F2>F1”: trials with F2 2Hz higher than F1, “F2<F1”: trials with F2 2Hz lower than F1.

Error bars correspond to SEM. \*\* $p < .005$ .

### Time-order effect

Both groups exhibited a TOE (Fig 3). The  $I_{TOE}$  was found significantly higher in the ASD group than in the NT ( $47$  vs.  $30$ ,  $p < .01$ ). Importantly, the ASD group was highly homogenous, as only two ASD subjects scored slightly below the median  $I_{TOE}$  of the NT group (median:  $27$ ). The two-way nested ANOVA of group and blocks (4 and 5) on the  $I_{TOE}$  revealed a group effect ( $F(1,31) = 10$ ,  $p < .01$ ) but no block effect, nor interaction between group and block.

### Posterior estimates of model parameters

In context-setting blocks,  $\beta$  did not differ between groups (NT:  $1.8 \pm 0.4$ , ASD:  $1.7 \pm 0.4$ ), and was strongly and positively correlated with the accuracy in these blocks ( $r = .98$ ,  $p < 10^{-6}$ ).  $\beta$  was also strongly and positively correlated with  $\pi_S$  estimated from TOE blocks ( $r = .83$ ,  $p < 10^{-6}$ ).

In TOE blocks, precision parameter  $\pi_S$  did not differ between groups ( $10.5 \pm 5.3$ , ASD:  $9.4 \pm 3.6$ ). However, TOE parameter  $\gamma$  was significantly higher in the ASD than in the NT group ( $1.6 \pm 0.4$  vs.  $1.0 \pm 0.4$ ,  $p < .001$ ). The ANOVA investigating the effect of blocks (4 or 5) and group on  $\pi_S$  and  $\gamma$  revealed no effect on  $\pi_S$  but a group effect on  $\gamma$  ( $F(1,31) = 13$   $p <$

.001). Positive correlations were naturally found between  $\pi_5$  and accuracy ( $r = .93, p < 10^{-6}$ ), and between  $\gamma$  and  $I_{TOE}$  ( $r = .89, p < 10^{-6}$ ).

## Experiment 2

As in the previous experiment, the tactile detection intensity threshold did not differ between groups (NT: 0.6mA  $\pm$ 0.2, ASD: 0.5mA  $\pm$ 0.2).

### *Accuracy and reaction times*

- *Context setting blocks (1 to 3)*

The NT group achieved 81% ( $\pm$ 8) of correct answers, and the ASD group 78% ( $\pm$ 9). The average RT was 751ms ( $\pm$ 315) and 876ms ( $\pm$ 369) in the NT and ASD group, respectively. None of these differences is significant.

- *TOE blocks (4 and 5)*

The average percentage of correct answers and response times were 67% ( $\pm$ 6) and 718ms ( $\pm$ 318) in the NT group and 65% ( $\pm$ 7) and 797ms ( $\pm$ 358) in the ASD group. No significant differences were found between groups on either accuracy or RT. The intra-group pairwise comparison of blocks 4 and 5 did not reveal any difference in accuracy or RT, neither for NT nor ASD subjects.

### *Time-order effect*

The NT and ASD groups both showed a TOE (Fig. 4.A). In contrast with Experiment 1, the two groups did not differ in their  $I_{TOE}$  (NT: 43  $\pm$ 16, ASD: 41  $\pm$ 18).

### *Model comparison to reveal contextual priors*

We performed family model comparison, between a first model family stating that the prior mean frequency was equal or less than 26Hz (i.e. centered on the middle of the range of the TOE blocks or below), and a second model family stating that the prior mean frequency was greater than 27Hz, up to 30Hz (i.e. drawn towards the middle of the range of the previous context setting blocks). In block 4, the exceedance probability in favor of the first model was 0.96 in the NT group, and 0.36 in the ASD group (Fig. 4.B). In block 5, it was 0.99 in the NT group and 0.82 in the ASD group (Fig. 4.C). Within the ASD group, the subjects whose priors had not switched from the previous range to the new range in session 4 are the ones with the highest autistic quotient ( $p=.05$ ; “non-adapted” subgroup:  $n=11$ ,  $AQ=38 \pm 9$ ; “adapted” subgroup:  $n=6$ ,  $AQ=30 \pm 6$ ).

We performed a two-way ANOVA analysis of the individual posterior probability for the mean frequency (26Hz) between groups and blocks revealed a main effect of the factor group ( $F(1,36) = 11, p < .01$ ) but no effect of the block and no interaction between groups and blocks.

### Posterior estimates of model parameters

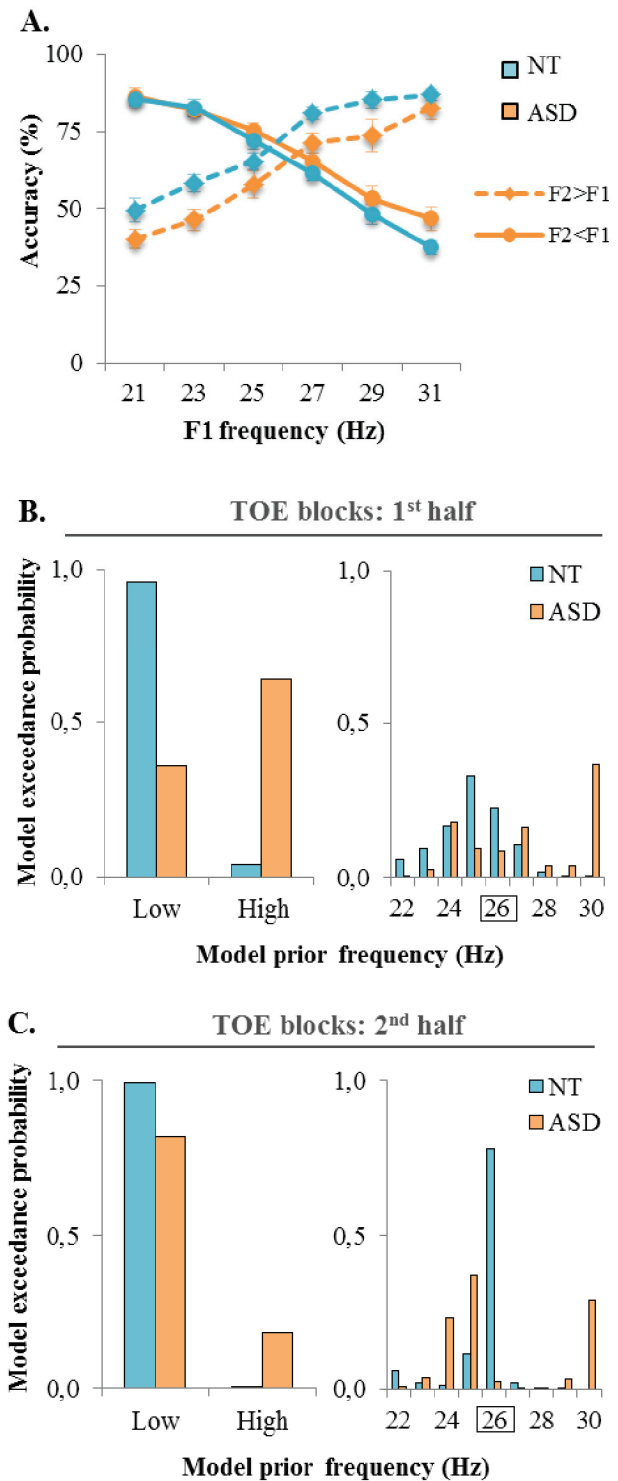
In the context setting blocks (SI, equation R3),  $\beta$  did not differ between groups (NT:  $1.8 \pm 0.5$ , ASD:  $1.7 \pm 0.6$ ). The parameter  $\beta$  was correlated with the mean accuracy ( $r = .98, p < 10^{-6}$ ), as well as with  $\pi_S$  from the TOE block ( $r = .74, p < 10^{-6}$ ).

Contrary to what was observed in Experiment 1, neither the precision parameter  $\pi_S$  nor the TOE parameter  $\gamma$  differed between groups (NT:  $\pi_S = 9.0 \pm 3.5$  and  $\gamma = 1.4 \pm 0.5$ ; ASD:  $\pi_S = 8.4 \pm 3.4$  and  $\gamma = 1.5 \pm 0.6$ ). Within group,  $\pi_S$  and  $\gamma$  did not significantly vary between block 4 and 5.

Finally,  $\pi_S$  positively correlated with the mean accuracy of the TOE blocks ( $r = .92, p < 10^{-6}$ ), and of the context setting blocks ( $r = .75, p < 10^{-6}$ ). In the TOE blocks,  $\gamma$  was also positively correlated with the  $I_{TOE}$  ( $r = .75, p < 10^{-6}$ ).

### Comparison between experiments 1 and 2

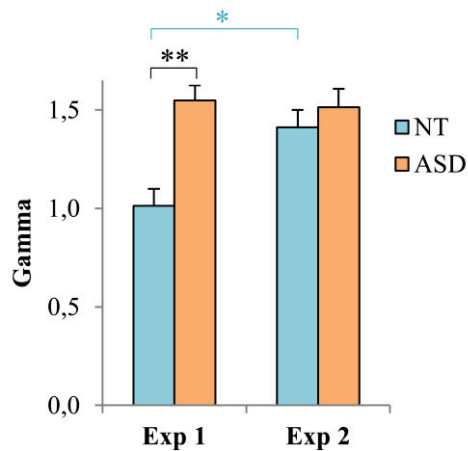
The NT group had a higher  $\gamma$  in Experiment 2 than in Experiment 1 ( $p < .01$ ) (Figure 5). Within the ASD group,  $\gamma$



**Figure 4: Experiment 2 – TOE in a changing context**  
**A.** Percentage of correct answers during the TOE blocks in the NT (blue) and ASD (orange) groups, for trials where  $F2$  was 2Hz higher ( $F2 > F1$ , dash line) or lower ( $F2 < F1$ , full line) than  $F1$ .

**B-C.** Model exceedance probability for the 1<sup>st</sup> (B) and 2<sup>nd</sup> (C) half of the TOE blocks. Left: Bayesian model comparison between two model families: low frequencies (current context) vs. high frequencies (former context). Right: details per frequency.

did not differ between the two experiments. Within group, there were no differences in accuracy and  $\pi_S$  between the two experiments.



**Figure 5: Gamma modulation according to the learning context**

Gamma estimation in Experiment 1 (stable context) and Experiment 2 (changing context) in the NT (blue) and ASD (orange) groups. Error bars correspond to the SEM. \*  $p < .01$ , \*\*  $p < .001$ .

### Post-experiment questionnaires

To the question “Did you have the impression that the frequency of the first stimulation was always the same?”, the subjects answering “yes” were 17% (Exp. 1) and 5% (Exp. 2) of the NT, and to 31% (Exp. 1) and 35% (Exp. 2) of the ASD. Only a few ASD subjects proved able to explicitly identify that it was during the three first blocks that F1 was never changing (3 individuals in Exp. 1, and 4 individuals in Exp. 2), while no NT were able to do so. Contrary to the NT, a majority of ASD subjects reported the impression that the intensity of the stimulation was stable over the blocks (66% on average in ASD vs. 34% in NT). The ASD subjects feeling a stable intensity showed a tendency toward less intra-individual variability in the threshold measurement (iiSD: 0.01 vs 0.17,  $p = .09$ ) as compared to the ones reporting a decreasing intensity. Finally, some subjects reported converting the tactile stimulus into an auditory one (rhythm or song) to help them discriminating and remembering the frequency (4 NT and 4 ASD in Exp. 1, 3 NT and 4 ASD in Exp. 2).

### Discussion

We used tactile discrimination tasks aiming at better characterizing perceptual inference in ASD. The presence of a TOE demonstrated that priors were implicitly built in both groups and influenced their perceptual decisions. The TOE had not been studied in ASD, but was widely studied in NT subjects (Preuschhof et al. 2010; Ashourian and Loewenstein 2011; Karim et al. 2013; Sanchez 2014) and in non-human primates (Romo et al. 1998, 2000; Harris et al. 2002; Romo and de Lafuente 2013). Experiment 1 showed that ASD subjects had

built “hyper-priors” in stable learning contexts relatively to NT. Experiment 2 revealed that both groups were able to adapt their priors to a new context, but the ASD group did it with a slower dynamic. Experiment 0 pointed out a reduced tactile adaptation in ASD. Note that the two groups did not differ in their tactile discrimination abilities nor in their average detection thresholds, consistently with previous findings on detection thresholds at 30Hz (Blakemore et al. 2006; Cascio et al. 2008; Puts et al. 2016).

### ***Strong prior weight on perception in stable contexts in ASD***

In Experiment 1, the stability of the learning context might have contributed to the build-up of very strong priors in ASD, relatively to NT. This was shown by increased  $\gamma$  and decreased response times in the ASD group, reflecting high confidence in their decisions. As suggested, “*rather than having uniformly weak priors, people with autism often develop very strong priors, or expectations, in particular contexts*” (Van de Cruys et al. 2013). In this stable context, hyper-priors can be seen as an over-specific learning of the context setting phase. This over-specific learning was also found in a behavioral task involving adults with ASD (Harris et al. 2015). Having very tight priors can explain categorization impairment if low variability is allowed between items and prototype (Church et al. 2010; Froehlich et al. 2012; Gastgeb et al. 2012), but also reduced perceptual flexibility (Ciesielski and Harris 1997; Robertson et al. 2013, 2016). These results showing hyper-priors in ASD is opposed to the proposal by Pellicano and colleagues suggesting hypo-priors in ASD (Pellicano and Burr 2012). In a predictive coding scheme, individuals with ASD may thus develop local hyper-priors (priors over priors such as the volatility of the environment (Robic et al. 2014).

Too narrow priors would quasi-systematically induce highly precise prediction errors, as predictions would almost always differ from the incoming sensory information (Van de Cruys et al. 2013). The fact that some ASD subjects (but no NT subjects) consciously perceived the change of experimental design between the context-setting blocks and TOE blocks signs for an acute detection of changes in ASD. This speaks in favor of a high precision of prediction errors in ASD which also fit with the existing literature on mismatch negativity (MMN) showing enhanced and/or earlier MMN responses in ASD (Ferri et al. 2003; Kujala et al. 2007; Cléry et al. 2013).



***No context-dependent modulation of prior weight in ASD***

The precision of the prediction error should be modulated according to the stability of the context: it should increase when there are new learnable regularities, and decrease in the presence of noise (Van de Cruys et al. 2013; Palmer et al. 2017). The NT group flexibly modulated the precision of prediction error when the stability of the context changed. Indeed, the change of frequency range in Experiment 2 led to an increased precision in the NT group, as compared to the more stable context of Experiment 1. In contrast, there was no context-dependent modulation of prior weight on perception in ASD. Similarly, the absence of adaptation in ASD also speaks for an impaired ability to flexibly suppress prediction errors, as opposed to NT.

***Slower prior adjustment in a changing context in ASD***

There was a slower dynamic of prior learning and adjustment in ASD, showed by the absence of adaptation in Experiment 0 and by the slower adjustment of priors in Experiment 2. Adaptation corresponds to a change in the adjustment of sensory systems to different levels of stimulation, according to prior experiment, leading to decreased neuronal firing (Whitsel et al. 2003; Schwiedrzik et al. 2014). As opposed to NT who must have been rapidly influenced by context, the ASD group might not have built up priors in this relatively short time lapse. Decreased tactile adaptation was previously shown in ASD (Tannan et al. 2008; Puts et al. 2014), and was linked to poor amplitude discrimination in NT subjects (Tannan et al. 2008). Adaptation decreases tactile frequency discrimination but enhances perception of change in a uniform sequence (Musall et al. 2014). Yet, in our experiments, there was no group difference in accuracy despite decreased adaptation in ASD as compared to NT. In a study showing that tactile spatial localization was not altered by prior tactile stimulation in ASD only (Tommerdahl et al. 2007), the authors suggested that it could be explained by a potential deficiency in GABAergic modulation when the period of adaptation is short (like in our threshold measurements).

Participants with ASD adapted their priors slower than controls when the context changed. The ASD group appeared to be much less flexible in the adjustment of their priors, and remarkably, this inflexibility was related to higher autistic quotients. Having very tight priors could contribute to reduced perceptual flexibility in ASD (Ciesielski and Harris 1997; Gomot and Wicker 2012; D’Cruz et al. 2013; Robertson et al. 2013; Van de Cruys et al. 2013; Robic et al. 2014; Robertson et al. 2016). Interestingly, a difference of dynamic was also

found in a study where ASD subjects learnt prototypical categories slower than NT (Vladusich et al. 2010), as items slightly differed from the prior. Another study showed slower perceptual learning in adults with ASD when the context changed, due to an over-specific learning of the prior context (Harris et al. 2015). This result is consistent with the idea that subjects with ASD could learn build up very strong priors when the context is stable, but would have difficulties updating these priors following a change in context.

However, a high precision of the prediction errors should be reflected by high learning rates in ASD (Palmer et al. 2017). In the predictive coding framework, this suggestion highlights that both causal hierarchy and volatility hierarchy should be considered to understand the dynamic of prior adjustment (Mathys et al. 2014; Palmer et al. 2017). ASD could be characterized by an overfit of the context leading to strong priors in stable contexts (in the causal hierarchy). Additionally, strong prior on the inflexibility of the environment (in the volatility hierarchy) could be associated with reduced context-dependent adjustment of priors and strong prediction errors. Indeed, in ASD, having strong priors on the stability of the context would be consistent with a decreased influence of priors in short time lapses (i.e. no adaptation in Experiment 0), a decreased adjustment of the prior mean (i.e. no flexible adjustment in frequency in Experiment 2), and a decreased adjustment of the prior weight in unstable contexts (i.e. no adjustment of  $\gamma$  in Experiment 2 vs. 1).

Our results show a reduced adaptation effect, strong priors in stable context and reduced adjustment of prior (i.e. weight and mean) in a changing context in ASD. These results show narrow priors at the lower levels of the causal hierarchy, and strong priors on the stability of the environment in the volatility hierarchy. A sub-optimal predictive coding system would deeply impair individuals in their social life as inferring others' behavior is crucial (Friston and Frith 2015). Further assessments should combine advanced dynamic computational models, informed task designs and neurophysiological measures in order to refine our understanding of perceptual inference in ASD.

## **References**

- American Psychiatric Association. 2013. Diagnostic and Statistical Manual of Mental Disorders, DSM Library. American Psychiatric Association.
- Ashourian P, Loewenstein Y. 2011. Bayesian inference underlies the contraction bias in delayed comparison tasks. *PLoS One*. 6:e19551.
- Baron-Cohen S, Wheelwright S, Robinson J, Woodbury-Smith M. 2005. The Adult Asperger Assessment (AAA): a diagnostic method. *J Autism Dev Disord*. 35:807–819.

- Baron-Cohen S, Wheelwright S, Skinner R, Martin J, Clubley E. 2001. The autism-spectrum quotient (AQ): evidence from Asperger syndrome/high-functioning autism, males and females, scientists and mathematicians. *J Autism Dev Disord.* 31:5–17.
- Biscaldi M, Rauh R, Irion L, Jung NH, Mall V, Fleischhaker C, Klein C. 2014. Deficits in motor abilities and developmental fractionation of imitation performance in high-functioning autism spectrum disorders. *Eur Child Adolesc Psychiatry.* 23:599–610.
- Blakemore S-J, Tavassoli T, Calò S, Thomas RM, Catmur C, Frith U, Haggard P. 2006. Tactile sensitivity in Asperger syndrome. *Brain Cogn.* 61:5–13.
- Brock J. 2012. Alternative Bayesian accounts of autistic perception: comment on Pellicano and Burr. *Trends Cogn Sci.* 16:573–574.
- Cascio C, McGlone F, Folger S, Tannan V, Baranek G, Pelphrey KA, Essick G. 2008. Tactile Perception in Adults with Autism: a Multidimensional Psychophysical Study. *J Autism Dev Disord.* 38:127–137.
- Church BA, Krauss MS, Lopata C, Toomey JA, Thomeer ML, Coutinho MV, Volker MA, Mercado E. 2010. Atypical Categorization in Children with High Functioning Autism Spectrum Disorder. *Psychon Bull Rev.* 17:862–868.
- Ciesielski KT, Harris RJ. 1997. Factors related to performance failure on executive tasks in autism. *Child Neuropsychol.* 3:1–12.
- Cléry H, Bonnet-Brilhault F, Lenoir P, Barthelemy C, Bruneau N, Gomot M. 2013. Atypical visual change processing in children with autism: an electrophysiological study. *Psychophysiology.* 50:240–252.
- Corbett JE, Venuti P, Melcher D. 2016. Perceptual Averaging in Individuals with Autism Spectrum Disorder. *Front Psychol.* 7:1735.
- Davis G, Plaisted-Grant K. 2015. Low endogenous neural noise in autism. *Autism Int J Res Pract.* 19:351–362.
- D’Cruz A-M, Ragozzino ME, Mosconi MW, Shrestha S, Cook EH, Sweeney JA. 2013. Reduced behavioral flexibility in autism spectrum disorders. *Neuropsychology.* 27:152–160.
- Ego C, Bonhomme L, Orban de Xivry J-J, Da Fonseca D, Lefèvre P, Masson GS, Deruelle C. 2016. Behavioral characterization of prediction and internal models in adolescents with autistic spectrum disorders. *Neuropsychologia.* 91:335–345.
- Ewbank MP, von dem Hagen EAH, Powell TE, Henson RN, Calder AJ. 2016. The effect of perceptual expectation on repetition suppression to faces is not modulated by variation in autistic traits. *Cortex J Devoted Study Nerv Syst Behav.* 80:51–60.
- Ferri R, Elia M, Agarwal N, Lanuzza B, Musumeci SA, Pennisi G. 2003. The mismatch negativity and the P3a components of the auditory event-related potentials in autistic low-functioning subjects. *Clin Neurophysiol Off J Int Fed Clin Neurophysiol.* 114:1671–1680.
- Fournier KA, Hass CJ, Naik SK, Lodha N, Cauraugh JH. 2010. Motor Coordination in Autism Spectrum Disorders: A Synthesis and Meta-Analysis. *J Autism Dev Disord.* 40:1227–1240.
- Friston K. 2003. Learning and inference in the brain. *Neural Netw Off J Int Neural Netw Soc.* 16:1325–1352.
- Friston K. 2016. The Bayesian Savant. *Biol Psychiatry.* 80:87–89.
- Friston K, Frith C. 2015. A Duet for one. *Conscious Cogn.*
- Friston KJ, Lawson R, Frith CD. 2013. On hyperpriors and hypopriors: comment on Pellicano and Burr. *Trends Cogn Sci.* 17:1.
- Froehlich AL, Anderson JS, Bigler ED, Miller JS, Lange NT, DuBray MB, Cooperrider JR, Cariello A, Nielsen JA, Lainhart JE. 2012. Intact prototype formation but impaired generalization in autism. *Res Autism Spectr Disord.* 6:921–930.
- García-Pérez MA. 1998. Forced-choice staircases with fixed step sizes: asymptotic and small-sample properties. *Vision Res.* 38:1861–1881.
- Gastgeb HZ, Dundas EM, Minschew NJ, Strauss MS. 2012. Category formation in autism: can individuals with autism form categories and prototypes of dot patterns? *J Autism Dev Disord.* 42:1694–1704.
- Gomot M, Wicker B. 2012. A challenging, unpredictable world for people with autism spectrum disorder. *Int J Psychophysiol Off J Int Organ Psychophysiol.* 83:240–247.
- Gowen E, Hamilton A. 2013. Motor abilities in autism: a review using a computational context. *J Autism Dev Disord.* 43:323–344.
- Green D, Charman T, Pickles A, Chandler S, Loucas T, Simonoff E, Baird G. 2009. Impairment in movement skills of children with autistic spectrum disorders. *Dev Med Child Neurol.* 51:311–316.

- Haker H, Schneebeli M, Stephan KE. 2016. Can Bayesian Theories of Autism Spectrum Disorder Help Improve Clinical Practice? *Front Psychiatry*. 7.
- Happé FG. 1996. Studying weak central coherence at low levels: children with autism do not succumb to visual illusions. A research note. *J Child Psychol Psychiatry*. 37:873–877.
- Harris H, Israeli D, Minshew N, Bonnef Y, Heeger DJ, Behrmann M, Sagi D. 2015. Perceptual learning in autism: over-specificity and possible remedies. *Nat Neurosci*. 18:1574–1576.
- Harris JA, Arabzadeh E, Fairhall AL, Benito C, Diamond ME. 2006. Factors Affecting Frequency Discrimination of Vibrotactile Stimuli: Implications for Cortical Encoding. *PLoS ONE*. 1.
- Harris JA, Miniussi C, Harris IM, Diamond ME. 2002. Transient Storage of a Tactile Memory Trace in Primary Somatosensory Cortex. *J Neurosci*. 22:8720–8725.
- Hollingworth HL. 1910. The Central Tendency of Judgment. *J Philos Psychol Sci Methods*. 7:461–469.
- Huys QJM, Maia TV, Frank MJ. 2016. Computational psychiatry as a bridge from neuroscience to clinical applications. *Nat Neurosci*. 19:404–413.
- Karaminis T, Cicchini GM, Neil L, Cappagli G, Aagten-Murphy D, Burr D, Pellicano E. 2016. Central tendency effects in time interval reproduction in autism. *Sci Rep*. 6:28570.
- Karim M, Harris JA, Langdon A, Breakspear M. 2013. The influence of prior experience and expected timing on vibrotactile discrimination. *Front Neurosci*. 7.
- Karim M, Harris JA, Morley JW, Breakspear M. 2012. Prior and Present Evidence: How Prior Experience Interacts with Present Information in a Perceptual Decision Making Task. *PLoS ONE*. 7:e37580.
- Kujala T, Aho E, Lepistö T, Jansson-Verkasalo E, Nieminen-von Wendt T, von Wendt L, Näätänen R. 2007. Atypical pattern of discriminating sound features in adults with Asperger syndrome as reflected by the mismatch negativity. *Biol Psychol*. 75:109–114.
- Lawson RP, Aylward J, White S, Rees G. 2015. A striking reduction of simple loudness adaptation in autism. *Sci Rep*. 5:16157.
- Lawson RP, Rees G, Friston KJ. 2014. An aberrant precision account of autism. *Front Hum Neurosci*. 8:302.
- Lord C, Rutter M, Goode S, Heemsbergen J, Jordan H, Mawhood L, Schopler E. 1989. Autism diagnostic observation schedule: a standardized observation of communicative and social behavior. *J Autism Dev Disord*. 19:185–212.
- Lord C, Rutter M, Le Couteur A. 1994. Autism Diagnostic Interview-Revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *J Autism Dev Disord*. 24:659–685.
- Mathys CD, Lomakina EI, Daunizeau J, Iglesias S, Brodersen KH, Friston KJ, Stephan KE. 2014. Uncertainty in perception and the Hierarchical Gaussian Filter. *Front Hum Neurosci*. 8.
- Miguel A García-Pérez RA-Q. 2011. Interval bias in 2AFC detection tasks: Sorting out the artifacts. *Atten Percept Amp Psychophys*. 73:2332–2352.
- Mitchell P, Mottron L, Soulières I, Ropar D. 2010. Susceptibility to the Shepard illusion in participants with autism: reduced top-down influences within perception? *Autism Res Off J Int Soc Autism Res*. 3:113–119.
- Mottron L, Belleville S, Ménard E. 1999. Local bias in autistic subjects as evidenced by graphic tasks: perceptual hierarchization or working memory deficit? *J Child Psychol Psychiatry*. 40:743–755.
- Mottron L, Dawson M, Soulières I, Hubert B, Burack J. 2006. Enhanced perceptual functioning in autism: an update, and eight principles of autistic perception. *J Autism Dev Disord*. 36:27–43.
- Musall S, von der Behrens W, Mayrhofer JM, Weber B, Helmchen F, Haiss F. 2014. Tactile frequency discrimination is enhanced by circumventing neocortical adaptation. *Nat Neurosci*. 17:1567–1573.
- Palmer CJ, Lawson RP, Hohwy J. 2017. Bayesian Approaches to Autism: Towards Volatility, Action, and Behavior. *Psychol Bull*.
- Pell PJ, Mareschal I, Calder AJ, von dem Hagen EAH, Clifford CWG, Baron-Cohen S, Ewbank MP. 2016. Intact priors for gaze direction in adults with high-functioning autism spectrum conditions. *Mol Autism*. 7:25.
- Pellicano E, Burr D. 2012. When the world becomes “too real”: a Bayesian explanation of autistic perception. *Trends Cogn Sci*. 16:504–510.
- Pleger B, Ruff CC, Blankenburg F, Bestmann S, Wiech K, Stephan KE, Capilla A, Friston KJ, Dolan RJ. 2006. Neural Coding of Tactile Decisions in the Human Prefrontal Cortex. *J Neurosci*. 26:12596–12601.

- Preuschhof C, Schubert T, Villringer A, Heekeren HR. 2010. Prior Information biases stimulus representations during vibrotactile decision making. *J Cogn Neurosci*. 22:875–887.
- Puts NAJ, Edden RAE, Evans CJ, McGlone F, McGonigle DJ. 2011. Regionally Specific Human GABA Concentration Correlates with Tactile Discrimination Thresholds. *J Neurosci*. 31:16556–16560.
- Puts NAJ, Wodka EL, Harris AD, Crocetti D, Tommerdahl M, Mostofsky SH, Edden RAE. 2016. Reduced GABA and altered somatosensory function in children with autism spectrum disorder. *Autism Res Off J Int Soc Autism Res*.
- Puts NAJ, Wodka EL, Tommerdahl M, Mostofsky SH, Edden RAE. 2014. Impaired tactile processing in children with autism spectrum disorder. *J Neurophysiol*. 111:1803–1811.
- Robertson AE, Simmons DR. 2013. The Relationship between Sensory Sensitivity and Autistic Traits in the General Population. *J Autism Dev Disord*. 43:775–784.
- Robertson CE, Kravitz DJ, Freyberg J, Baron-Cohen S, Baker CI. 2013. Slower Rate of Binocular Rivalry in Autism. *J Neurosci*. 33:16983–16991.
- Robertson CE, Ratai E-M, Kanwisher N. 2016. Reduced GABAergic Action in the Autistic Brain. *Curr Biol*. 26:80–85.
- Robic S, Sonié S, Fonlupt P, Henaff M-A, Touil N, Coricelli G, Mattout J, Schmitz C. 2014. Decision-Making in a Changing World: A Study in Autism Spectrum Disorders. *J Autism Dev Disord*.
- Romo R, de Lafuente V. 2013. Conversion of sensory signals into perceptual decisions. *Prog Neurobiol*. 103:41–75.
- Romo R, Hernández A, Zainos A, Brody CD, Lemus L. 2000. Sensing without Touching: Psychophysical Performance Based on Cortical Microstimulation. *Neuron*. 26:273–278.
- Romo R, Hernández A, Zainos A, Salinas E. 1998. Somatosensory discrimination based on cortical microstimulation. *Nature*. 392:387–390.
- Ropar D, Mitchell P. 2002. Shape constancy in autism: the role of prior knowledge and perspective cues. *J Child Psychol Psychiatry*. 43:647–653.
- Sanchez G. 2014. Real-Time Electrophysiology in Cognitive Neuroscience: Towards Adaptive Paradigms to study perceptual Learning and Decision-Making in Humans. PhD Thesis Claude Bernard Lyon 1 Univ Fr.
- Schmitz C, Martineau J, Barthélémy C, Assaiante C. 2003. Motor control and children with autism: deficit of anticipatory function? *Neurosci Lett*. 348:17–20.
- Schwiedrzik CM, Ruff CC, Lazar A, Leitner FC, Singer W, Melloni L. 2014. Untangling Perceptual Memory: Hysteresis and Adaptation Map into Separate Cortical Networks. *Cereb Cortex N Y NY*. 24:1152–1164.
- Sinclair RJ, Burton H. 1996. Discrimination of vibrotactile frequencies in a delayed pair comparison task. *Percept Psychophys*. 58:680–692.
- Sinha P, Kjelgaard MM, Gandhi TK, Tsourides K, Cardinaux AL, Pantazis D, Diamond SP, Held RM. 2014. Autism as a disorder of prediction. *Proc Natl Acad Sci U S A*. 111:15220–15225.
- Stephan KE, Iglesias S, Heinzle J, Diaconescu AO. 2015. Translational Perspectives for Computational Neuroimaging. *Neuron*. 87:716–732.
- Summerfield C, Trittschuh EH, Monti JM, Mesulam MM, Egnér T. 2008. Neural repetition suppression reflects fulfilled perceptual expectations. *Nat Neurosci*. 11:1004–1006.
- Tannan V, Holden JK, Zhang Z, Baranek GT, Tommerdahl MA. 2008. Perceptual metrics of individuals with autism provide evidence for disinhibition. *Autism Res Off J Int Soc Autism Res*. 1:223–230.
- Tommerdahl M, Tannan V, Cascio CJ, Baranek GT, Whitsel BL. 2007. Vibrotactile adaptation fails to enhance spatial localization in adults with autism. *Brain Res*. 1154:116–123.
- Van de Cruys S, de-Wit L, Evers K, Boets B, Wagemans J. 2013. Weak priors versus overfitting of predictions in autism: Reply to Pellicano and Burr (TICS, 2012). *Percept*. 4:95–97.
- Van de Cruys S, Evers K, Van der Hallen R, Van Eylen L, Boets B, de-Wit L, Wagemans J. 2014. Precise minds in uncertain worlds: predictive coding in autism. *Psychol Rev*. 121:649–675.
- Vladusich T, Olu-Lafe O, Kim D-S, Tager-Flusberg H, Grossberg S. 2010. Prototypical category learning in high-functioning autism. *Autism Res Off J Int Soc Autism Res*. 3:226–236.
- Whitsel BL, Kelly EF, Quibrera M, Tommerdahl M, Li Y, Favorov OV, Xu M, Metz CB. 2003. Time-dependence of SI RA neuron response to cutaneous flutter stimulation. *Somatosens Mot Res*. 20:45–69.

## *Supplementary information*

### ***SI-1: Bayesian model of two-interval forced choices***

We developed a generative probabilistic model of trial-wise decisions (Sanchez 2014) in two-alternative forced choice (2AFC) tasks (also called two-interval forced choice (2ICF) experiments (García-Pérez 2011)). Regardless of the sensory modality, this model is concerned with trials where a first stimulus S1 is presented, followed by a delay period and then a second stimulus S2 which the subject has to compare with S1 along the instructed feature dimension of interest (here: the frequency). The subject's answer can only be of two sorts: either S1 was perceived as larger or as smaller than S2.

The model is made of two components, a perceptual and a decision one. The perceptual part which applies twice, once for each stimulation, conforms to a simple though generic Bayesian inference scheme (Mathys et al. 2014). The decision rule is the one of a rational agent under perceptual uncertainty and conforms to optimality in the sense of signal detection theory.

Importantly, this model accounts for the time-order effect (TOE), namely the effect of presentation order of the paired stimuli on accuracy. It is well-known that subjects perform better when the first stimulus lies between the second stimulus and the global mean of all stimuli along the judged dimension compared to the reverse order (Karim et al. 2012). This effect is independent of the sensory modality and can be massive (Preuschhof et al. 2010). It is thought to reflect the influence of acquired priors built on the recent history of perceived stimulations during the task (Karim et al. 2012). This influence affects the perception of the first stimulation more strongly because of the delay period during which this percept has to be maintained in working memory (Ashourian and Loewenstein 2011).

### **Perceptual model**

The perceptual component is concerned with the inference of the feature of interest when presented with a single stimulation. In a Bayesian framework, perception of stimulus  $s$  results from the combination of sensory evidence (likelihood) and *prior* belief. Without loss of generality one can consider Gaussian distributions for both the *prior* and likelihood functions:

$$s \sim N(\theta, 1/\pi_s) \quad (1)$$

and

$$\theta \sim N(\theta_0, 1/\pi_\theta) \quad (2)$$

where  $s$  refers to the (noisy) sensory input in log-space<sup>5</sup>,  $\theta$  is the hidden feature amplitude to be inferred,  $\pi_s$  is the precision attributed to the sensory input, while  $\theta_0$  and  $\pi_\theta$  indicate the *prior* mean and precision, respectively.

The ensuing percept is then also encoded by a Gaussian distribution and results from applying Bayes rule as follows:

$$\theta|s \sim N(\mu, 1/\pi_{\theta|s}) \quad (3)$$

where  $\mu$  and  $\pi_{\theta|s}$  indicate the posterior mean and precision, which follow from applying Bayes rule and write

$$\begin{aligned} \pi_{\theta|s} &= \pi_\theta + \pi_s \\ \mu &= \frac{\pi_\theta \cdot \theta_0 + \pi_s \cdot s}{\pi_{\theta|s}} \end{aligned} \quad (4)$$

Interestingly, the posterior mean also writes

$$\mu = \theta_0 + \frac{\pi_s}{\pi_{\theta|s}} \cdot (s - \theta_0) \quad (5)$$

which reads as belief up-dating by adding a weighted prediction error term to the *prior* mean (Mathys et al. 2014).

Another way to write the posterior means  $\mu_1$  and  $\mu_2$  for stimulus 1 and 2 respectively is

$$\mu_1 = \theta_0 + \frac{1}{1+r+\Delta r} (s_1 - \theta_0) \quad \mu_2 = \theta_0 + \frac{1}{1+r} (s_2 - \theta_0) \quad (6)$$

with the ratio between *prior* precision and likelihood precision

$$r = \frac{\pi_{\theta_2}}{\pi_s} \quad r_1 = \frac{\pi_{\theta_1}}{\pi_s} = r + \Delta r \quad \Delta r > 0 \quad (7)$$

Here, we make the assumption that the precision  $\pi_s$  is the same for the two stimulations.

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<sup>5</sup> In agreement with the Weber-Fechner law

**Decision model**

Given the posterior over stimulations  $s_1$  and  $s_2$ , the probability  $p_a$  of answering that  $s_1$  is larger than  $s_2$  writes as follows (Ashourian and Loewenstein 2011):

$$\begin{aligned} p_a &= p(\mu_1 > \mu_2 | s_1, s_2) = \int_{-\infty}^{\infty} p(\mu'_1 | s_1) \int_{-\infty}^{\mu'_1} p(\mu'_2 | s_2) d\mu'_1 d\mu'_2 \\ &= \frac{1}{2} \cdot \left( 1 + \operatorname{erf}\left(\frac{1}{\sqrt{2}} \cdot R\right) \right) \end{aligned} \quad (8)$$

with  $\operatorname{erf}$  indicating the Gauss error function.

Finally, ratio  $R$  is given by

$$R = \frac{\pi_{\theta_1 | s_1} \cdot \pi_{\theta_2 | s_2}}{\pi_{\theta_1 | s_1} + \pi_{\theta_2 | s_2}} \cdot (\mu_1 - \mu_2) \quad (9)$$

The error function is monotonic such that  $p_a$  increases with  $R$ . If  $R$  is equal to zero, the probability  $p_a$  of choosing  $s_1$  is at chance level. Note that  $R$ , like a  $d'$  measure or a  $t$  statistics, is a ratio between a difference in (conditional) means and a variance component. In other words, the probability of choosing  $s_1$  scales as a function of both the expectation about the difference between the two stimuli and the precision or confidence about this expectation.

Applying equation (6) to the difference between  $\mu_1$  and  $\mu_2$  gives

$$\mu_1 - \mu_2 = \frac{1}{1+r} \cdot \frac{1}{1+\gamma} [(s_1 - s_2) - \gamma(s_2 - \theta_0)] \quad (10)$$

$$\text{with } \gamma = \frac{\Delta r}{1+r} = \frac{r_1 - r_2}{1+r_2}$$

Increases in  $\gamma$  will be associated with increases in the amplitude of the TOE. Indeed, when  $\gamma$  increases, the comparison between the second stimulation  $s_2$  and the prior is given a high weight.

Moreover, the first term of equation (9) can be written as:

$$\frac{\pi_{\theta_1 | s_1} \cdot \pi_{\theta_2 | s_2}}{\pi_{\theta_1 | s_1} + \pi_{\theta_2 | s_2}} = \pi_S \cdot (1+r) \cdot \frac{1+\gamma}{2+\gamma} \quad (11)$$

The combination of equations (10) and (11) in the equation (9) gives:



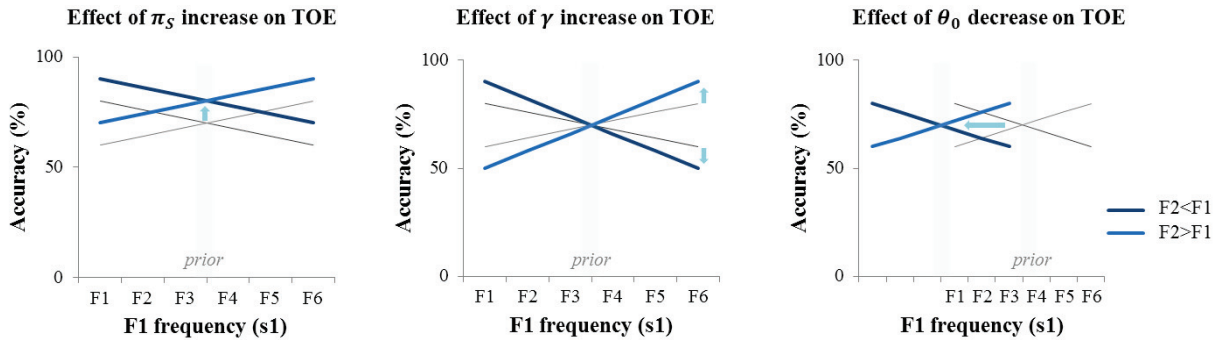
$$R_1 = \frac{\pi_S}{2 + \gamma} [(s_1 - s_2) - \gamma(s_2 - \theta_0)] \quad (12)$$

$$R_2 = \frac{\pi_S(1 + \gamma)}{2 + \gamma} \left[ (s_1 - s_2) - \frac{\gamma}{1 + \gamma} (s_1 - \theta_0) \right]$$

$$\text{If } s_1 = \theta_0 \quad R_3 = \beta(s_1 - s_2)$$

$$\text{with } \beta = \frac{\pi_S(1 + \gamma)}{2 + \gamma}$$

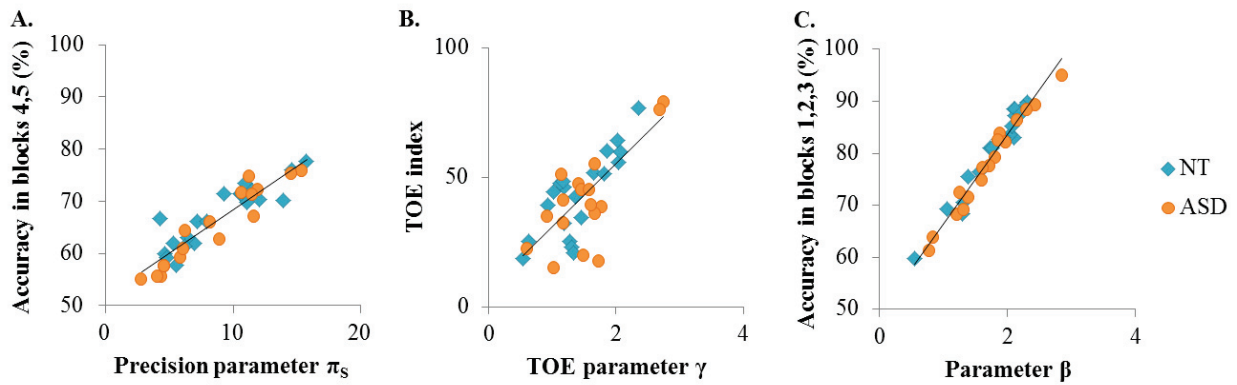
The first term into brackets is simply the objective difference between  $s_1$  and  $s_2$ . The second term into brackets corresponds to the error of prediction for the second stimulus, weighted by the parameter  $\gamma$ . The higher  $\gamma$ , the larger the TOE. The whole term is weighted by the precision  $\pi_S$  of the encoding of the stimulations and by the coefficient  $\gamma$ . An increased coefficient  $\gamma$  corresponds either to  $\pi_{\theta_1} \gg \pi_{\theta_2}$  or to a decreased precision  $\pi_S$ .



#### ***Schematic predictions about the modulation of the model parameters***

*Toy illustration of show the main effects of the three parameters in the TOE discrimination task. The grey lines correspond to a standard TOE, while blue lines correspond to the modification of the TOE following the increase of  $\pi_S$  or  $\gamma$ , or following a decrease in  $\theta_0$ . The clear blue arrow indicates the main change.*

In our study, we used the VBA toolbox to fit the data (<http://mbb-team.github.io/VBA-toolbox/>) and estimate the parameters  $\pi_S$  and  $\gamma$ .  $\pi_S$  and  $\gamma$  were set as the exponential of the parameters P1 and P2, whose *priors* were respectively  $\log(3)$  and  $\log(1)$ . The parameters  $\pi_S$  and  $\gamma$  were then averaged within groups using Bayesian model averaging (BMA), with 10 000 samplings of these values.

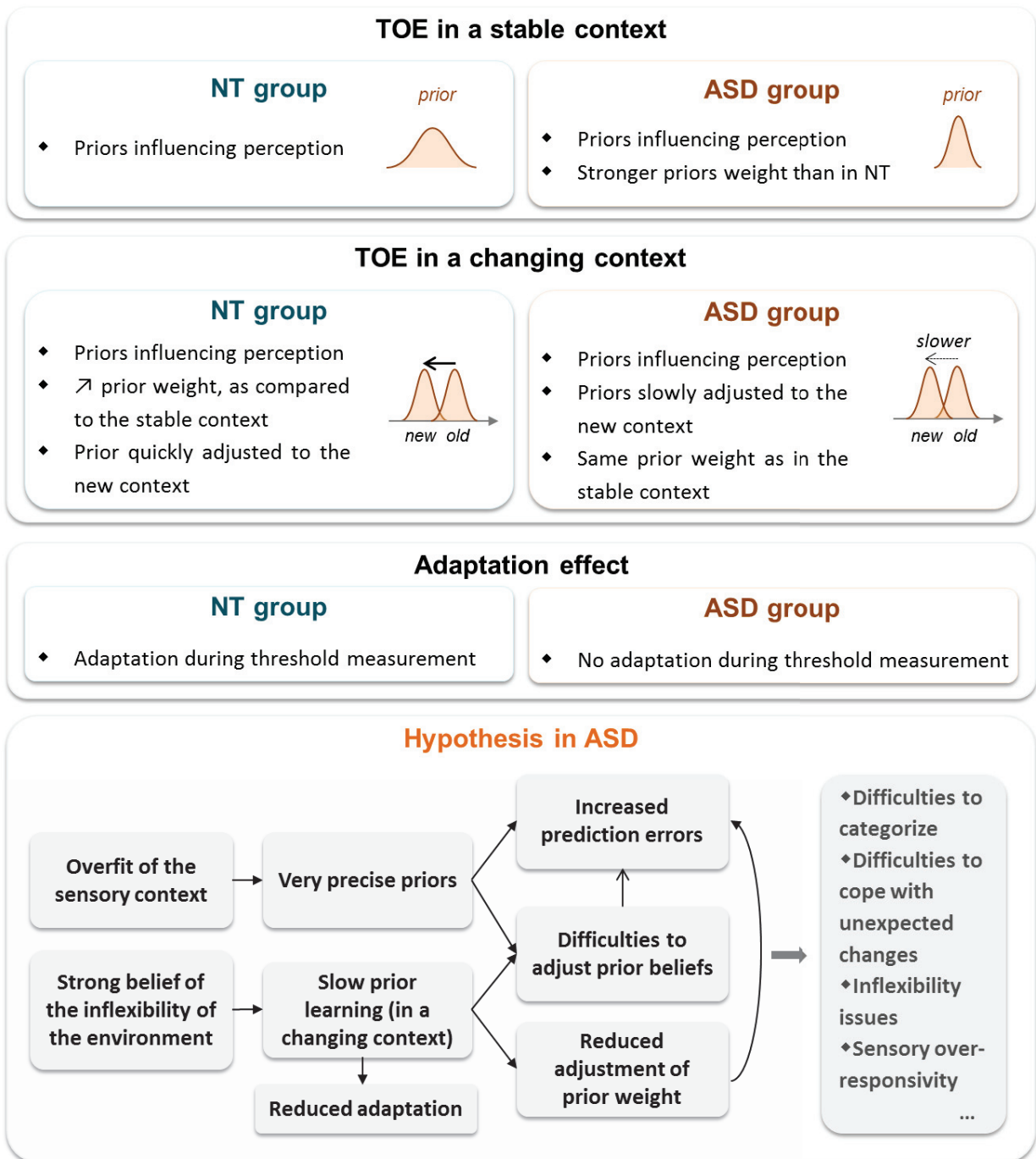


**Correlations between the estimated model parameters and data (Experiment 2)**

Bayesian model averaging was performed to estimate two parameters:  $\pi_s$ , supposed to reflect the precision of the encoding and  $\gamma$ , supposed to reflect the TOE in the TOE blocks, and the parameter  $\beta$  in the context-setting blocks.

- A.** Correlation between the individual accuracy and parameter  $\pi_s$  in the TOE blocks (4 and 5) ( $r = .92, p < 10^{-6}$ ).
- B.** Correlation between the amplitude of the TOE and parameter  $\gamma$  in the TOE blocks (4 and 5) ( $r = .75, p < 10^{-6}$ ).
- C.** Correlation between the individual accuracy and the precision parameter  $\beta$  in the context-setting blocks (1 to 3) ( $r = .95, p < 10^{-6}$ ).

## Synthesis



## IV. Study IV: Neural underpinnings of perception in ASD

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### *Preamble*

*« I think I am ready: I have been listening to the MRI sounds that you sent me, really often over the past month, so as to get used to them. »*

*Participant with ASD (H.M.) before the MRI session*

*« Does my brain look very autistic? I mean, which part is so special? »*

*Participant with ASD (L.B.) when I showed her a picture of her structural MRI*

*« Enthusiastic! I have rarely been feeling so enthusiastic and peaceful »*

*Participant with ASD (G.B.), after 90 minutes of MRI*

Even though every participant was obviously not feeling as enthusiastic as patient G.B., subjects with and without ASD were involved in an MRI study. This study aimed at better characterizing perception within the Bayesian framework at the behavioral, neuronal population, and molecular levels. At the behavioral level, we tested the time-order effect (TOE) in a changing context, without a prior phase of stable learning. At the neural level, we investigated the correlates of this tactile discrimination task, and most importantly, studied the regions whose activity was modulated by prediction errors, and by prior weights onto perceptual decisions. At the molecular level, we explored whether an atypical balance in Glutamate and GABA could explain the atypical perception.

Our fMRI study was designed to elicit a TOE in a tactile discrimination task. Here, we used a different stimulator than during the previous behavioral study: an MRI-compatible piezoelectric stimulator instead of an electric stimulator. We assessed the TOE in a context where the mean frequency was changing three times over the course of the experiment. We applied our computational model to estimate the precision of sensory encoding, the nature and the influence of prior beliefs.

This fMRI study was based on a study by Preuschhof and colleagues, who investigated the neural modulation associated with the time-order effect in control participants (Preuschhof et al. 2010). Preuschhof and colleagues performed a tactile discrimination task using fMRI, in which they investigated the effect of two parametric modulators. The first modulator P1 reflected the difference between the first stimulation and the prior (i.e. the prediction error on the first stimulus), and the second modulator P2 reflected the subjective difficulty of the discrimination task, induced by the prior (Preuschhof et al. 2010). Their results are shown in

Figure 36. The first modulator P1 induced modulations of the activity of the somatosensory cortex, thalamus, inferior frontal gyrus, and inferior parietal gyrus, while the second modulator had an effect on the anterior cingulate cortex activity.

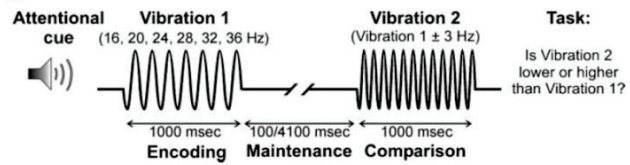
We aimed at replicating these findings in NT individuals, and at investigating the neural correlates of prediction error and prior influence in subjects with ASD. According to the high and inflexible precision of prediction error in autism (HIPPEA) hypothesis, an

inflexible precision should be reflected by a decreased modulation of P1 in the ASD group. The key regions for prior and prediction error encoding, and so, where we could expect group differences are the IFG, the inferior parietal lobe, the orbitofrontal cortex, the cerebellum, the ACC, the striatum and insula.

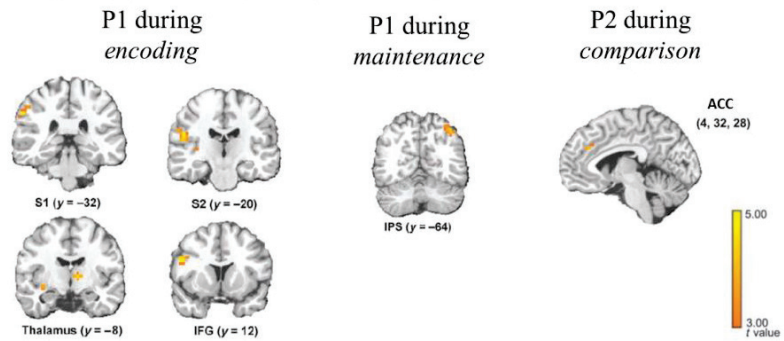
At the molecular level, predictive coding suggests that the prediction error would be encoded by a ratio between glutamate and GABA, and would be modulated by acetylcholine and norepinephrine (Lawson et al. 2014; Van de Cruys et al. 2014). Magnetic resonance spectroscopy (MRS) enables the measurement of glutamate and GABA concentrations. Unfortunately, it does not give access to acetylcholine and norepinephrine measurements. We used single voxel MRS in a volume of interest encompassing the primary and secondary somatosensory cortices. The goal was to assess whether glutamate and GABA concentrations would have a different relationship with measures of sensory precision and prior weighting in ASD and NT groups, respectively.

**Figure 36 : Results of the fMRI time-order effect task by Preuschhof et al. 2010**

**A. Design**



**B. Parametric modulation by P1 and P2**



*A. Design of their tactile discrimination task*

*B. Left and middle: Brain regions in which the BOLD signal reflects the difference between F1 frequency and the average frequency during encoding and maintenance. Right: brain region in which the BOLD signal is modulated by the subjective difficulty provoked by the prior. Activation clusters shown at  $p < .003$  uncorrected (MNI space) S1 and S2: primary and secondary somatosensory cortices; IFG: inferior frontal gyrus; IPS: intraparietal sulcus; ACC: anterior cingulate cortex.*

## *Functional MRI study*

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### Neurophysiological underpinnings of perceptual inference in ASD

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#### *Abstract*

Perceptual inference relies on the idea that percepts result from the weighted interplay between received sensory information and expected sensations (priors). Discrepancies between sensory inputs and priors generate prediction errors. In autism spectrum disorder (ASD), there is growing evidence that atypical perceptual inference could explain symptoms such as decreased global processing, increased bottom-up processing or flexibility difficulties. The current study aimed at better characterizing prior adjustment and prediction error precision modulation in ASD, at the behavioral and neural levels.

22 neurotypicals (NT) and 21 participants with ASD were involved in an fMRI study. They performed a tactile discrimination task designed to elicit a time-order effect (TOE), illustrating the effect of priors on perceptual decisions.

Both groups implicitly learnt a prior, as seen by their TOE. Yet, the ASD group had difficulties adjusting their priors in changing contexts. The size of the prediction error modulated neural activity in the somatosensory cortices, inferior parietal and prefrontal regions in both groups, and this modulation was stronger in the inferior frontal gyrus of NT. During the decision-making process, increases in subjective difficulty induced by priors was reflected by increased activity in the anterior cingulate cortex and cerebellum in NT, and by increased activity of inferior parietal and prefrontal regions in the ASD group.

These results are in favor of an atypical perceptual inference in ASD with decreased flexibility to adjust priors. Further analyses including dynamic causal modeling on these fMRI data are needed to refine the understanding of prediction error weighting in ASD.

## *Introduction*

In a fluctuant and complex environment, we need to learn its main underlying characteristics to be optimally adapted. These internal representations help inferring the meaning of surrounding stimulations, and detecting important changes from random noise. These internal references, or priors, are learnt over our past experience. Priors influence our perception, in a way that percepts reflect the interplay of current sensory inputs and prior knowledge. Indeed, the Bayesian framework states that percepts emerge from the combination of weighted sensory information and prior beliefs. A percept can be more or less biased toward priors depending on the relative precision (or weight) of sensory information and priors. For instance, perception will be greatly distorted toward priors if one has very strong priors and/or receive very noisy sensory inputs. Under prior influence, sensory information look closer to priors than it actually is (Hollingworth 1910; Preuschhof et al. 2006; Ashourian and Loewenstein 2011). Having priors adapted to specific contexts enables to minimize mismatches between expectations and actual sensory inputs, therefore allowing a better adaptation to the environment.

Prediction errors correspond to these discrepancies between priors and sensory inputs. Receiving permanent strong prediction errors would lead to constant surprise, maladapted priors, difficulties to interpolate between stimuli to generalize, etc. With inflexible priors, one would try to avoid novelty and keep a very strict daily routine in order to avoid unexpected changes. Such an atypical weighting of priors and sensory inputs could explain the symptoms encountered in autism spectrum disorder (ASD), a neurodevelopmental disorder affecting 1 in 68 children (Christensen et al. 2016). ASD is characterized by difficulties in social interactions and social communication, and by restricted and repetitive patterns of behaviors (American Psychiatric Association 2013). Atypical perceptual inference in ASD was suggested a few years ago (Brock 2012; Pellicano and Burr 2012; Lawson et al. 2014; Van de Cruys et al. 2014). Hypotheses in ASD included too blurred priors (Pellicano and Burr 2012), too precise sensory inputs (Brock 2012), atypical precision ratio between priors and sensory inputs (Lawson et al. 2014) leading to high and inflexible precision of the prediction error in autism (HIPPEA) (Van de Cruys et al. 2014).

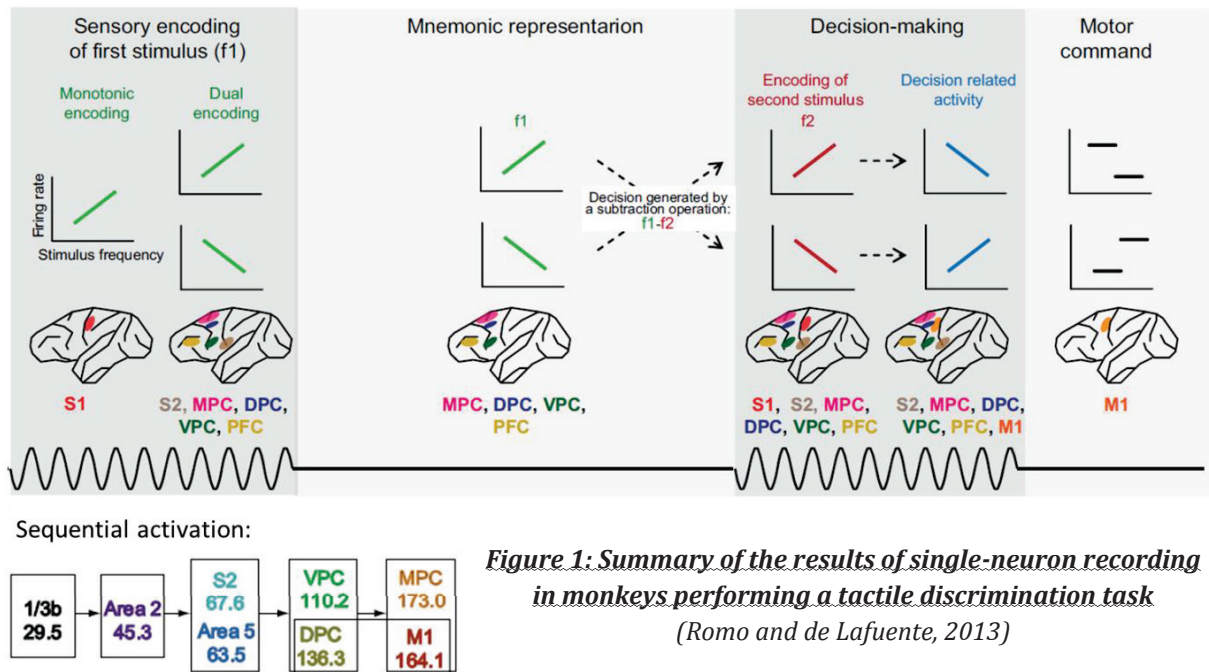
In previous behavioral experiments (Experimental results - III), we showed that individuals with ASD were able to build up priors in stable learning contexts, but had troubles adjusting them quickly when the context was changing. Using computational models, we showed that ASD participants had built very precise priors. Importantly, in the ASD group,

the precision of the prediction error did not appear to be modulated by the stability of the learning context, contrary to neurotypical (NT) participants. In order to investigate the implicit build-up of priors, we made use of the time-order effect (TOE), by which the subjective difference between two successive stimulations can be over- or under-estimated depending on the order of presentation of the stimuli. The TOE reminds of the Central Theory of Judgment (Hollingworth 1910), whereby the percept of memorized stimuli were biased toward the prior. In TOE tasks, two stimuli are successively presented (e.g., vibrotactile stimulations), and the magnitude of one of their features has to be compared (e.g., their frequencies). Previous works showed that the perception of the first stimulus is even more biased toward the prior than the second one, as it has to be kept into memory during a certain delay (Ashourian and Loewenstein 2011; Karim et al. 2013). This perceptual bias can be seen both in accuracy and response times, and has been previously shown in the tactile modality (Harris et al. 2006; Karim et al. 2013; Preuschhof et al. 2006, 2010; Romo et al. 2000; Sinclair and Burton 1996). A large literature informs on the TOE in the tactile modality in human and non-human primates (Romo and de Lafuente 2013).

Indeed, the neural processes involved in tactile frequency discrimination tasks have been studied in control participants with neuroimaging techniques (Harris et al. 2002; Pleger et al. 2006; Preuschhof et al. 2006, 2010; Kostopoulos et al. 2007; Sörös et al. 2007; Tang et al. 2009; Auksztulewicz et al. 2011; Kalberlah et al. 2013; Pleger and Villringer 2013; Herding et al. 2016) and in non-human primates using single-unit recording (Mountcastle et al. 1990; Romo et al. 1998, 1998; Hernández et al. 1997, 2000, 2002; Salinas et al. 2000; Brody et al. 2002; Luna et al. 2005; Lemus et al. 2007; Camarillo et al. 2012; Romo and de Lafuente 2013; Vázquez et al. 2013; Rossi-Pool et al. 2016). Results from these studies enabled to propose a chain of neural processes for tactile discrimination, involving the encoding of F1 followed by its maintenance, the encoding of F2 and comparison with the memory trace of F1. Sensory information first arrives to the contralateral primary sensory cortex (S1) through the thalamus, and passes to bilateral secondary somatosensory cortex (S2), inferior parietal lobe and inferior frontal gyrus (Kostopoulos et al. 2007). Precisely, single-unit recording studies showed that F1 frequency modulated the activity of S1 neurons during the encoding phase only, of S2 neurons during the encoding and the first hundred milliseconds of the maintenance period, of the PFC neurons during the encoding and maintenance period, and of neurons in the ventral, medial and dorsal premotor cortex (PMC) in the encoding and maintenance period. To sum up, during the encoding phase, information would be encoded in S1 and distributed to S2, ventral, medial, dorsal premotor cortex and



PFC, and during the maintenance, the premotor and PFC regions would maintain F1 representation (Figure 1).



**Figure 1: Summary of the results of single-neuron recording in monkeys performing a tactile discrimination task**  
(Romo and de Lafuente, 2013)

Brain regions in macaques: VPC: ventral premotor cortex (~ IFG opercularis / precentral gyrus), DPC: dorsal premotor cortex (~ middle frontal gyrus), MPC: medial premotor cortex (~ dorsolateral superior frontal gyrus/SMA), PFC: prefrontal cortex (~IFG triangularis), M1: primary motor cortex.

Among the studies listed above, one investigated the brain regions whose activity was modulated by prior encoding and influence on perceptual decision (Preuschhof et al. 2010). They evidenced that during the encoding and maintenance of the first stimulus (F1), neural activities in S1 and S2, thalamus, inferior frontal gyrus (IFG) and inferior parietal sulcus (IPS) were modulated by the difference between the prior (mean frequency) and F1. Between participants, a greater influence of priors on decision was associated with greater activity in IPS (angular gyrus). Furthermore, the activity in the anterior cingulate cortex (ACC) was modulated by the subjective difficulty induced by the TOE (Preuschhof et al. 2010).

Besides, an EEG study using a vibrotactile discrimination task showed that F1 modulated beta activity in the IFG during the maintenance period (Spitzer et al. 2010). The role of the IFG in the maintenance of F1 representation was confirmed by a transcranial magnetic stimulation protocol disrupting the activity of the IFG during the maintenance period (Aukstulewicz et al. 2011). Such a disruption (in any hemisphere) led to decreased accuracy, therefore showing that the IFG played a key role in the maintenance of somatosensory information. Another EEG study showed that participant's choices modulated beta activity in the dorsal PMC (Herding et al. 2016). This result suggests that the comparison between F2 and the memory trace of F1 would be computed in this region (overlapping the

dorsolateral superior frontal gyrus and the supplementary motor area) (Herding et al. 2016). Single-neuron recording also showed that the activity of some PMC neurons was modulated by the type of answer (F2 superior or inferior to F1) (Romo and de Lafuente 2013). Interestingly, the PMC was pointed out in another single-neuron recording study showing that PMC neurons encode the frequency pattern as broad categories during the maintenance and comparison periods, and that the initial “*sensory representation is transformed into an intermediate, more abstract categorical code that combines past and present information to ultimately generate a perceptually informed choice*” (Rossi-Pool et al. 2016).

Here, we performed an fMRI study using a tactile discrimination task designed to elicit a time-order effect. The present study aimed to (1) confirm previous findings showing that individuals with ASD are able to build up priors, but have difficulties to adjust them in a changing context, (2) identify the cerebral network involved in the TOE task in NT and ASD participants, (3) replicate the finding by Preuschhof et al. (2010) in NT participants on the parametric modulation of brain activity by the priors, and (4) determine whether the ASD participants present with a different modulation of their brain activity by prior and prediction error weights. Aim (1) was studied with a time-order task where the context suddenly changed, and was characterized using computational modeling. We expected the ASD group to be less flexible in the construction and measurement of their priors, despite similar accuracy in both groups. Aim (2) was investigated with a simple functional MRI analysis of TOE trials versus control trials, and a functional connectivity analysis. We also investigated the regions whose activity was inter-individually modulated by sensory input precision and prior influence, with covariate analyses using the parameters estimated by the models. No specific differences between groups were expected for the cerebral pattern reflecting simple tactile discrimination tasks. Aims (3) and (4) were investigated using the same parametric modulators as Preuschhof and colleagues (Preuschhof et al. 2010). The parametric modulator representing the discrepancy between the expectation (average frequency) and the incoming sensory input should modulate the activity of somatosensory regions, the IFG and IPS in the NT group (Preuschhof et al. 2010). This discrepancy between the prior and the sensory evidence can be seen as a prediction error on the first stimulation. According to HIPPEA hypothesis (Van de Cruys et al. 2014), the modulation of the precision of the prediction error should be reduced within the ASD group, which could be seen as a decreased modulation in the ASD group, especially in regions like the IFG and IPS. During the decision phase, we expect the activity in the ACC to be modulated by the subjective difficulty (reflected by the TOE) in the NT group (Preuschhof et al. 2010).

## Material and Methods

### Participants

Twenty-two NT adults and twenty adults with ASD took part to this study. In addition, one subject with ASD was discarded from the fMRI and behavioral analyses as he only made one of the four fMRI runs (because of the unpleasant noise of the fMRI sequence). The two groups were matched for age, gender, educational level, and IQ (measured by the Weschler Adult Intelligence Scale IV). The demographical characteristics are given in Table 1.

All participants with ASD met

<i>Demographical data</i>			
	NT	ASD	p
<b>Number</b>	22	20	-
<b>Male / Female</b>	16 / 6	14 / 6	<i>ns</i>
<b>Age (years)</b>	32.8 ( $\pm$ 8.2)	34.4 ( $\pm$ 9.6)	<i>ns</i>
<b>Educational level (years)</b>	4.1 ( $\pm$ 2.3)	3.3 ( $\pm$ 2.4)	<i>ns</i>
<b>Right/Left-handed</b>	18 / 4	16 / 4	<i>ns</i>
<b>WAIS IV</b>			
<i>Total<sup>#</sup></i>	120 ( $\pm$ 12)	124 ( $\pm$ 20)	<i>ns</i>
<i>Verbal comprehension</i>	126 ( $\pm$ 12)	128 ( $\pm$ 15)	<i>ns</i>
<i>Perceptual reasoning</i>	112 ( $\pm$ 12)	110 ( $\pm$ 18)	<i>ns</i>
<i>Working memory</i>	113 ( $\pm$ 11)	110 ( $\pm$ 17)	<i>ns</i>
<i>Processing speed</i>	107 ( $\pm$ 5)	105 ( $\pm$ 23)	<i>ns</i>
<b>AQ score</b>	12 ( $\pm$ 5)	34 ( $\pm$ 8)	***
<b>GSQ score</b>			
<i>Total</i>	40 ( $\pm$ 17)	69 ( $\pm$ 20)	**
<i>Total hyposensitivity</i>	20 ( $\pm$ 8)	31 ( $\pm$ 9)	**
<i>Tactile hyposensitivity</i>	4 ( $\pm$ 2)	5 ( $\pm$ 2)	<i>ns</i>
<i>Total hypersensitivity</i>	21 ( $\pm$ 10)	38 ( $\pm$ 13)	**
<i>Tactile hypersensitivity</i>	3 ( $\pm$ 2)	6 ( $\pm$ 3)	*

Diagnostic and Statistical Manual of Mental Disorders-IV criteria for Asperger's syndrome or high-functioning autism. Every participant with ASD was diagnosed by an expert psychiatrist, and underwent the Autism Diagnostic Observation Schedule (ADOS) (Lord et al. 2000), the Autism Diagnostic Interview-Revised (ADI-R) (Lord et al. 1994), or Adult Asperger Assessment (Baron-Cohen et al. 2005). None of the NT participants reported mental health or neurological disorders. All participants had normal or corrected-to-normal vision. Participants signed a written consent and were remunerated for their participation. Approval was obtained from the local ethics committee (South East IV Committee for the Protection of Persons).

### Session

Prior to the fMRI experiment, participants were introduced to the task with oral and written instructions. Outside the MRI room, participants first performed tactile threshold measurements, as well as a training and a familiarization task of tactile frequency discrimination. Participants were then placed in the MRI scanner where they performed similar tasks successively: threshold measurements, training session, four tactile frequency discrimination tasks and threshold measurements. The overall session proceeding is shown in

Figure 2. The part outside the MRI scanner lasted for 20 minutes on average. The MRI acquisition lasted for 1.5 hour.

### ***Tactile stimuli***

Tactile stimulations were delivered on the left second finger, using an fMRI-compatible piezo-electric tactile stimulator (mPTS, Dancer Design <http://www.dancerdesign.co.uk>). Each stimulator was housed in a machined ceramic case 67mm long x 20mm wide x 5mm thick. The vibrating surface was a 6mm diameter flat aluminum probe in the center of an 8mm diameter hole in one end of the case. Two stimulators were placed in a home-made polystyrene case, with only the probes showing up on the surface. Participants wore a fingerless glove bonding on the case, with the distal phalanges of the left second and fourth finger resting on the stimulator. The two stimulated fingers were immobilized using Velcro strips. Tactile and visual stimuli were displayed using Presentation (<https://www.neurobs.com/> 17.1 03.15.14).

### ***Tactile threshold measurement***

In order to adapt the amplitude of tactile stimulations in each subject, perception thresholds were measured. The tactile detection threshold was estimated in each subject following a classical staircase procedure (García-Pérez 1998). The tactile intensity progressively increased, and participants had to signal by a click when they started to feel the sensation. Then, the intensity kept on increasing up to 1.5 times the intensity presented when the participant clicked. The intensity then decreased, and participants signaled by a click when they did not feel any sensation any more. The frequency of the stimulations remained at 30Hz, and intensity increased and decreased by steps of 0.050. This procedure (increase/decrease) was repeated four times successively. The tactile threshold was measured prior to the familiarization task. For the discrimination tasks, the amplitude of the stimulations was set to 3 times the threshold for the familiarization task and to 3.5 times the threshold for the fMRI session.

### ***Discrimination task***

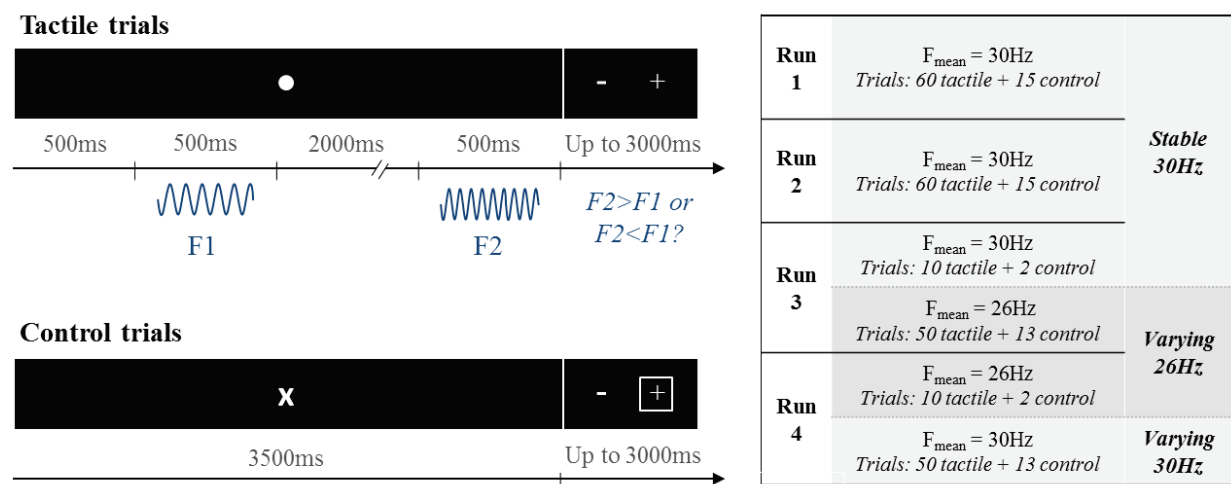
The experiment was made of two types of trials: 80% of tactile trials (announced by a disc display) and 20% of control trials (announced by a cross display) (Figure 2). The inter-trial interval lasted for 1800ms on average (ranging from 1500ms to 2100ms).

### Tactile trials

In the tactile trials, participants received two successive tactile stimulations on the second finger to be compared. They had to determine whether the frequency of the second vibration was higher or lower than the first one. In tactile trials, after 500ms of grey disk display, a first 500ms vibration was delivered. It was followed by a 2000ms pause, and then by a second 500ms vibration. The response screen appeared right after the second stimulation, and showed plus and minus signs on each side of the screen. The side of the plus and minus signs were counterbalanced between participants, but never changed within a task in order not to disturb participants. Participants had to press on the left or right button to select the left or right sign. They were asked to always compare the second frequency  $F_2$  to the first frequency  $F_1$  (e.g. select the minus sign if the second frequency was lower than the first one). Participants had up to 3000ms to answer. In training tasks only, a feedback was provided after each trial, displaying “correct” or “incorrect” for 800ms.

### Control trials

In the control trials, no tactile stimulations were delivered. A cross was displayed for 3500ms, followed by a response screen where the plus sign or the minus sign was circled. Participants had to click on the side of the circled sign. Participants had up to 3000ms to answer. In training tasks only, a feedback was provided after each trial, displaying “correct” or “incorrect” for 800ms.



**Figure 2: Experimental design**

The left part of the figure presents the tactile trials (top) and control trials (bottom). In tactile trials, participants have to compare the frequency of two successively delivered tactile stimulations. In control trials, participants simply have to click on the side of the circled sign (here, on the right side).  $F_1$ : first frequency,  $F_2$ : second frequency.

The right part of the figure presents the overall fMRI session, made of four runs.

## ***Experimental procedure***

### *Training 1 and Familiarization task*

In training 1 and the familiarization task, the frequency of the first vibration was always equal to 30Hz. The second vibration was 1 to 8Hz higher or lower than F1, therefore ranging from 22 to 38Hz. Training 1 was made of 20 trials: 4 control trials and 16 tactile trials presenting each couple of frequency once. The Familiarization session consisted of 72 trials: 8 control trials and 64 tactile trials presenting each couple of frequency four times.

### *Training 2 and fMRI runs*

Training 2 consisted of 12 trials: 2 control trials and 10 tactile trials with F1 equal to 30Hz and F2 equal to 20, 22, 24, 26, 28, 32, 34, 36, 38 or 40Hz.

Each fMRI run was composed of 75 trials, including 15 control trials and 60 tactile trials. At every trial, the frequency of the second stimulation (F2) was 2Hz higher or lower than F1. Runs 1 and 2 are referred as “stable runs”, centered on a frequency of 30Hz. Runs 3 and 4 are referred as “unstable runs” as the average frequency varied. In run 3, the 12 first trials were centered on 30Hz, but the next trials were centered on 26Hz. In run 4, the 12 first trials were centered on 26Hz, but the next trials were centered on 30Hz.

In sections centered on 30Hz (run 1, run 2, beginning of run 3, end of run 4), F1 was equal to 22, 26, 30, 34 or 38Hz. In sections centered on 26Hz (end of run 3, and beginning of run 4), F1 was equal to 18, 22, 26, 30, or 34Hz.

## ***Computational modeling***

A probabilistic model of the TOE was used to estimate the sensory precision  $\pi_S$  and the TOE coefficient  $\gamma$ . This model is the same as in the behavioral study (Supplementary material of Experimental results, III). We used Bayesian model comparison with prior mean  $\theta_0$  ranging from 24 to 32Hz. We fitted each model independently for each subject in each group. We ran a Bayesian Model Selection (BMS) in SPM12, to compare three model families: Model 26Hz (with frequencies from 24 to 26Hz), Model intermediate (with frequencies from 27 to 29Hz), and Model 30Hz (with frequencies from 30 to 32Hz). BMS resulted in an exceedance probability for each model and each group. We also extracted the frequencies with the maximal posterior probability for each subject. We performed Bayesian model comparison in the 30Hz section (75 + 75 + 12 trials of Run 1, 2, and 3), of the variable 26Hz session (63 + 12 trials of Run 3 and 4), and of the variable 30Hz session (63 trials of Run 4).

We used the VBA toolbox to fit the data (<http://mbb-team.github.io/VBA-toolbox/>) and estimate  $\pi_L$  and  $\gamma$ . The parameters  $\pi_L$  and  $\gamma$  were then averaged within groups using Bayesian model averaging (BMA), to be weighted by the posterior probability of each prior frequency.

### ***Specific behavioral measures***

Apart from accuracy and response times, we characterized two other measures: the time-order effect index  $I_{TOE}$ , and the flexibility value.

The TOE is reflected by a biased perceptual decision: the difference between the two frequencies will be over- or under-estimated depending on the trials. For trials with frequencies below the prior (average frequency), it leads to increased accuracy with shorter response times when  $F2 < F1$ , whereas it leads to decreased accuracy with longer response times when  $F2 > F1$ . The TOE can be quantified as follows. For each possible value of  $F1$ , we compute the difference in accuracy between the trials with  $F2 > F1$  and with  $F2 < F1$  (e.g. 22-24Hz vs. 22-20Hz). Averaged over all  $F1$  values and divided by the individual mean accuracy, this yields what we refer to as  $I_{TOE}$ . The  $I_{TOE}$  should be strongly positively correlated with the estimated  $\gamma$  parameter.

The flexibility value measures the ability of the participant to flexibly adjust its prior depending on the context. Given the experimental design, the priors should be  $\theta_A = 30\text{Hz}$  (during the 30Hz stable runs),  $\theta_B = 26\text{Hz}$  (during the 26Hz variable run), and  $\theta_C = 30\text{Hz}$  (during the 30Hz variable run). The flexibility parameter  $\varphi$  is calculated as  $[(\theta_A - \theta_B) + (\theta_C - \theta_B)]$ . It should be equal to 8Hz in case of an optimal adjustment of the prior, and to 0Hz if the prior was not adjusted across the four sessions.

### ***Behavioral data analysis***

Demographical data in the two groups were compared using Student t-test. Group differences were investigated with Analysis of Variance (ANOVA). Correlations were studied using Pearson correlation tests. Unanswered trials were not taken into account in the analyses.

All statistical analyses were performed using R (<http://www.r-project.org/>). The threshold for statistical significance was set at  $p < .05$  for the behavioral analyses.

### ***Functional MRI***

#### ***fMRI data acquisition***

Neuroimaging data were collected on a 3 Tesla Siemens Magnetom Prisma with a 64-channel head-neck coil. The MRI acquisition started with a high resolution whole brain T1-

weighted anatomical image MPRAGE sequence, TR = 3500ms; TE = 3.42ms; FOV = 224mm; number of slices = 192; voxel size = 0.9 x 0.9 x 0.9 mm). Participants then engaged a training session and four functional scans (around 7.5min each, separated by 2-minute breaks). Whole brain functional images were acquired using a multi-band T2-weighted echoplanar imaging sequence sensitive to BOLD contrast (TR = 1500 ms; TE = 29 ms; flip angle = 75°; FOV = 230mm; number of interleaved slices = 48 ; voxel size = 2.3 x 2.3 x 2.3 mm; multi-band accelerator factor = 2; PAT mode = GRAPPA). The total number of volumes acquired during a functional run differed between participants as it depended on the individual response time. On average, 308 functional volumes were acquired per run.

Every participant had four runs acquired, except for four ASD participants: one only had one run, one had two runs, and two had three runs.

### ***fMRI data preprocessing***

Neuroimaging data were preprocessed using Nipype Python (Gorgolewski et al. 2011) and SPM12 (<http://www.fil.ion.ucl.ac.uk/spm/>). The first five functional volumes of each run were removed so as to ensure that longitudinal relaxation time equilibration was achieved. Preprocessing consisted of fieldmap correction, realignment of the functional volumes, slice-timing correction, coregistration, normalization, and smoothing. Functional volumes realigned and coregistered on the anatomical T1. The artifact detection toolbox (ART) detected the scans with more than 3mm of movement, and these were considered as outliers. Participants with more than 10% of scans discarded were excluded from the analysis. This criterion led to the exclusion of two ASD participants. In the other participants, the average number of outlier scans was 1.0% in the NT, and 1.5% in the ASD group. The slice-timing correction for multiband sequence was implemented as provided by SPM12 (with slice acquisition times). Functional and anatomical volumes were normalized into the Montreal Neurological Institute (MNI), with the anatomical volume as source image. Finally, volumes were smoothed with a 7 mm full-width at half-maximum Gaussian kernel. After preprocessing, an additional step of denoising was added using aCompCor, performing a principal component analysis on CSF and white matter masks in order to remove physiological noise (Behzadi et al. 2007).

### ***fMRI data analysis***

Functional MRI data were analyzed with Matlab 2016a and SPM12 (<http://www.fil.ion.ucl.ac.uk/spm/software/spm12/>), coordinated with nipype (<http://nipype.org/nipype/0.10.0/>). We performed two main analyses: the trial type analysis and the parametric modulator analysis. Statistical analyses were based on a General Linear Model.



In all analyses, the six movement parameters, the five components estimated by aCompCor, and the scans detected by Art were added as regressors of non-interest. The epoch of the regressors were convolved with a canonical hemodynamic function. Low-frequency drift were removed using a temporal high-pass filter (128sec). Unanswered trials were discarded from the analysis.

#### *Trial type analysis*

This analysis aimed to study the network involved in the tactile discrimination task, and its modulation between participants depending on covariates estimated from the Bayesian modeling. We defined three regressors: the tactile trial regressor, the control trial regressor, and the motor response. The tactile trial regressor started at the beginning of the tactile trial marked by the disc display, and lasted until the participant answer. It lasted for 3500ms plus the response time. The control trial regressor started at the beginning of the control trial marked by the cross display, and lasted until the participant answer. It lasted for 3500ms plus the response time. The motor response regressor corresponded to the event where the participant clicked to answer. Contrast images were computed for the tactile trial regressor versus control trials for each subject using t statistics. NT and ASD groups were compared using Student t test.

We further compared the tactile trials in stable runs (1 and 2) versus unstable runs (3 and 4) in order to show the modulations due to the stability of the context.

#### *Parametric modulator analysis*

This analysis aimed to study the brain regions whose activity was related to the time-order effect. We used four regressors and two parametric modulators: the *Encoding regressor*, the *Comparison regressor*, the *Control response screen regressor*, the *Motor response regressor*, the *Encoding modulator P1*, and the *Comparison modulator P2*. The *Encoding regressor* started at the beginning of the first vibration F1 and lasted until the end of the maintenance period (500ms + 2000ms). The *Comparison regressor* started at the beginning of the second vibration and lasted until an answer was given (500ms + response time) in tactile trials. The *Control response screen regressor* started at the beginning of the appearance of the response screen in control trials and lasted until an answer was given. The *Motor response regressor* corresponds to the event where the participant clicked on one of the response button (in tactile and control trials). The *Control response screen regressor* and *Motor response regressor* are regressors of non-interest, but were modeled to be removed from the baseline.

We additionally specified parametric modulations of the Encoding and Comparison regressors, based on Preuschhoff and colleagues study (Preuschhoff et al. 2010). We defined the values of these parametric modulators as Preuschhoff and colleagues did.

P1 parametric modulation represents the activity of the brain regions involved in the integration of the frequency of the first vibration during the encoding and maintenance of this frequency. During the encoding of F1 and the maintenance period, the representation of F1 is thought to be drifted toward the prior (average frequency). The further F1 is from the prior, the larger this drift toward the prior will be. P1 was calculated as the absolute value of the difference between the first frequency F1 and the average frequency of the session (30Hz or 26Hz, depending on the run section). The resulting values (0, 4, 8) defined the parametric modulation of the Encoding regressor. P1 can also be seen as the prediction error between the frequency of the first vibration and the frequency of the prior.

P2 parametric modulation corresponds to the activity of the brain regions involved in the comparison of the two frequencies when the perception is biased by priors. Precisely, it reflects the difficulty of the comparison given the time-order effect. The TOE shows that when frequencies lie below the average frequency (prior), decision is facilitated for trials were  $F2 < F1$ , but is harder for trials were  $F2 > F1$ . Conversely, when frequencies lie above the average frequency (prior), decision is facilitated for trials were  $F2 > F1$  but is harder for trials were  $F2 < F1$ . This effect is relatively increased when F2 is further from the prior. P2 was calculated as follows: the absolute difference between F2 and the prior was first calculated (equal to 2, 6, or 10Hz). If F1 lied below the prior, this absolute difference was attributed a minus sign for trials were  $F2 < F1$ , and was given a plus sign when  $F2 > F1$ . Conversely, if F1 lied above the prior, this absolute difference was attributed a minus sign for trials were  $F2 > F1$ , and was given a plus sign when  $F2 < F1$ . When F1 was equal to the average frequency, it was set to 0. Hence, very easy trials (22-20Hz, 38-40Hz) were attributed -10, easy trials (26-24Hz, 34-36Hz) were attributed -6, neutral trials (30-32Hz, 30-28Hz) were attributed 0, difficult trials (26-28Hz, 34-32Hz) were attributed 2, and very difficult trials (22-24Hz, 38-36Hz) were attributed 6.

The resulting values (-10, -6, 0, 2, 6) defined the parametric modulation P2 of the Comparison regressor. We assessed the effects of P1 on the Encoding regressor and of P2 on the comparison regressor, as compared to baseline, and between groups.

*Covariate analyses*

In the trial type and parametric modulator analysis, we assessed the effect of three covariates: the TOE parameter  $\gamma$ , the precision parameter  $\pi_L$ , and the flexibility parameter  $\phi$ . We investigated the regions whose activity was showing a positive or negative covariance with these parameters, and masked the results with the contrast results. To illustrate these correlations, we extracted the individual contrast estimates in the clusters identified in the covariate analyses, using Marsbar (<https://sourceforge.net/projects/marsbar>).

*Significance threshold for fMRI analyses*

In the trial type analysis, parametric modulator analysis, and covariate analysis, statistical significance was set at  $p < .001$  uncorrected at the voxel level (with 10 contiguous voxels), and at  $p < .05$  at the cluster level. In the analyses, it is specified whether the clusters survive FWE correction.

***Functional connectivity***

We performed a simple functional connectivity analysis using Nipype, and modeling the tactile trials regressor. We chose nine regions of interest, corresponding to the regions highlighted in Preuschhof et al. (2010) study: contralateral S1, bilateral S2, IFG opercularis, IPG and ACC. Seed coordinates were chosen based on the results by Preuschhof et al (2010), except for S1 and the ACC which were selected using anatomical criteria. We used 15 mm spheres centered on right S1 (MNI: 52, -26, 50), right/left S2 (MNI: +/-52, -20 20), right/left IFG (MNI: +/-52, 12, 24), right/left IPG (MNI: +/-40, -64, 48) and right/left ACC (+/-10, 34, 20). Time series were extracted by averaging signal of voxels within these ROIs, high pass filtered at 0.01Hz regressed out of white matter and CSF average signals and normalized. Weighted correlations (Dodel et al. 2005) between time series of these regions weighted by the regressor tactile trials were performed in each participant. For the two groups (NT and ASD groups) r-to-Z Fisher's transform were applied to weighted correlation coefficients. One-way Student t-test was performed over the Z scores of each pair, and results were corrected using Bonferroni correction ( $\alpha=0.001$ ). The two groups were compared using two-way Student t-test, and results were corrected using Bonferroni correction ( $\alpha=0.001$ ).

## Results

### **Behavioral results**

#### ***Perceptual tactile threshold***

Prior to the familiarization task, the average threshold of perception was equal to  $0.45 \pm 0.19$  in the NT group, and to  $0.34 \pm 0.13$  in the ASD group who had a lower threshold ( $p = 0.03$ ). Prior to the fMRI session, the average threshold was  $0.44 \pm 0.21$  in the NT group, and  $0.42 \pm 0.19$  in the ASD group, and their thresholds did not differ significantly.

#### ***Behavioral tasks (prior to fMRI)***

##### *Training*

In the training session, the NT group got 80.2% ( $\pm 11.2$ ) of correct answers, and the ASD group 74.4% ( $\pm 9.8$ ). No group difference was observed on accuracy, but the NT group answered faster than the ASD group ( $843.7\text{ms} \pm 306.8$  vs  $1122.5\text{ms} \pm 273.8$ ,  $p < .005$ ).

##### *Familiarization*

During the familiarization, the NT group performed better ( $p < .05$ ) and faster ( $p < .01$ ) than the ASD group. The mean accuracy and response times were equal to 84.7% ( $\pm 10.2$ ) and 696.7ms ( $\pm 281.5$ ) in the NT group, and to 75.7% ( $\pm 13.1$ ) and 940.8ms ( $\pm 210.6$ ) in the ASD group.

The two-way ANOVA analysis of the group and difficulty factor (8 levels, from 1 to 8Hz of difference between F1 and F2) on accuracy revealed a main effect of the group factor ( $F(1,42) = 45.4$ ,  $p < 10^{-6}$ ), of the difficulty factor ( $F(1,42) = 23.4$ ,  $p < 10^{-6}$ ), but no interaction between the factors group and difficulty.

Both groups got 100% of correct answers for the control trials, with average response times of 658.4ms ( $\pm 147.1$ ) in the NT group, and 790.8ms ( $\pm 168.4$ ) in the ASD group.

### ***fMRI behavioral results***

#### ***Training***

During the training phase, NT participants got 89.4%  $\pm 12.9$  of correct answers, and ASD participants got 82.9% ( $\pm 14.5$ ) of correct answers. The average response time was 587.1ms ( $\pm 224.7$ ) in the NT group, and 712.3ms ( $\pm 190.0$ ) in the ASD group. The two groups did not significantly differ in accuracy and response times, but there was a tendency toward longer response times in ASD than NT ( $p = .055$ ).

***Accuracy and response times in the fMRI runs***

During the fMRI sessions, the average rate of correct answers and the response times were 64.8% ( $\pm 6.9$ ) and 657.6ms ( $\pm 246.8$ ) in the NT group, and 59.7% ( $\pm 8.8$ ) and 809.1ms ( $\pm 187.5$ ) in the ASD group. There was a tendency toward a lower accuracy in ASD than NT ( $p = .05$ ), and longer response times ( $p = .055$ ). The rate of correct answers for control trials was 100% for all subjects. The NT group answered faster than the ASD group for the control trials (605.4ms  $\pm 99.4$  vs. 708.1ms  $\pm 97.7$ ,  $p < .01$ ). On average, NT participants answered to 99.8% of the trials, and ASD participants to 98.9% of the trials.

A 2x4 ANOVA analysis of the factors group and session on accuracy and response times for correct answers revealed a group effect (accuracy:  $F(1,42) = 30.9$ ,  $p < 10^{-6}$ ; RTc:  $F(1,42) = 70.3$ ,  $p < 10^{-6}$ ) but no session effect, and no interaction between session and group.

In the stable 30Hz part, the NT and ASD group performed comparably (NT: 64.7%  $\pm 6.1$ , ASD: 59.6%  $\pm 9.0$ ). No group difference in accuracy were revealed in the changing 26Hz part (NT: 66.7%  $\pm 9.3$ , ASD: 61.2%  $\pm 10.2$ ), nor in the changing 30Hz part (NT: 64.5%  $\pm 9.2$ , ASD: 59.1%  $\pm 11.4$ ).

***TOE index during the fMRI runs***

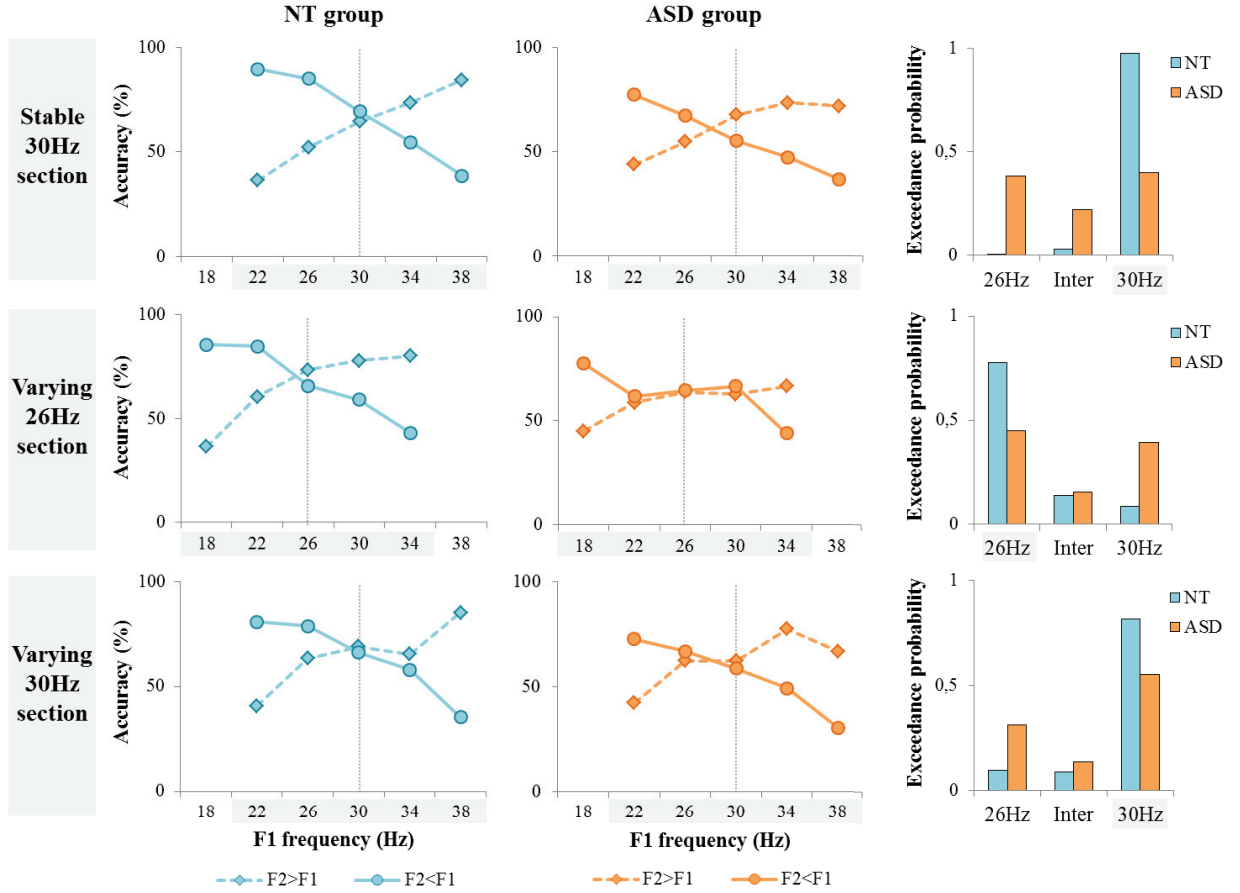
Both the NT and ASD group showed a TOE effect in every section of the fMRI run, as shown by a positive  $I_{TOE}$  (NT:  $I_{TOE}=54 \pm 24$ , ASD:  $I_{TOE}=38 \pm 32$ ). The ANOVA analysis of the factors group and run (3 kinds) on the  $I_{TOE}$  showed no group effect, a run effect ( $F(2,74) = 4.0$ ,  $p < .05$ ), and an interaction between run and group ( $F(2,74) = 3.8$ ,  $p < .05$ ). The ASD group had a lower  $I_{TOE}$  in the 26Hz variable section than the NT group (NT:  $I_{TOE}=50 \pm 27$ , ASD:  $I_{TOE}=22 \pm 34$ ,  $p < .01$ ).

***Model comparison to study contextual priors***

We performed family model comparison in each section of the fMRI, between three model families: the first stating that the prior mean frequency  $\theta_0$  was between 24 and 26Hz (*26Hz model*), the second stating that  $\theta_0$  was between 27 and 29Hz (*Intermediate model*), and the third stating that  $\theta_0$  was between 30 and 32Hz (*30Hz model*). The TOE and model comparisons are shown in Figure 3.

In the 30Hz stable section, the exceedance probability in favor of the third model (*30Hz model*) was 0.97 in the NT group and 0.40 in the ASD group. In the 26Hz variable section, the exceedance probability in favor of the first model (*26Hz model*) was 0.78 in the NT group and 0.45 in the ASD group. In the 30Hz varying section, the exceedance probability in favor of the third model (*30Hz model*) was 0.82 in the NT and 0.55 in the ASD group.

The flexibility parameter  $\phi$ , equal to 8Hz in theory, was 5Hz in the NT group and 2Hz in the ASD group. The participants with a  $\phi$  under 4Hz were 41% of the NT group, and 70% of the ASD group.



**Figure 3: Time-order effect in the fMRI session, with Bayesian model selection**

The left graphics present the mean accuracy in the NT and ASD groups, when  $F_2$  is 2Hz higher than  $F_1$  (dash line) or 2Hz lower than  $F_1$  (full line), for each  $F_1$  frequency. The mean frequency is 30Hz in the first row (Stable 30Hz section: 130 tactile trials), 26Hz in the second row (Varying 26Hz section: 60 tactile trials), and 30Hz in the third row (Varying 30Hz section: 50 tactile trials).

The right graphics show the model exceedance probability of the Bayesian model selection in these three sections of the fMRI session. A Bayesian model comparison was performed between three model families: 26Hz prior model (24 to 26Hz), Intermediate prior model (27 to 29Hz), and 30Hz prior model (30 to 32Hz).

NT group: blue, ASD group: orange.  $F_1/F_2$ : frequency of the first/second stimulation.

### Posterior estimates of model parameters

In the 30Hz stable runs, 26Hz variable runs, and 30Hz variable run, respectively,  $\pi_S$  was equal to 8.3 ( $\pm 3.9$ ), to 6.3 ( $\pm 3.1$ ), and to 5.8 ( $\pm 2.6$ ) in the NT group, and to 6.8 ( $\pm 4.6$ ), to 4.7 ( $\pm 2.3$ ), and to 5.4 ( $\pm 2.6$ ) in the ASD group. Within the NT group,  $\pi_S$  was higher in the

30Hz stable runs than in the 30Hz variable run ( $p < .01$ ). Within the ASD group,  $\pi_S$  was higher in the 30Hz stable runs than in the 26Hz variable run ( $p < .05$ ). The ANOVA analysis of the factor group and run (3 kinds of run) on  $\pi_S$  revealed no group effect, a run effect ( $F(2,74) = 8.7, p < .001$ ), and no interaction between group and run.  $\pi_S$  was positively correlated with accuracy in the 30Hz stable runs ( $r = .8, p < 10^{-6}$ ), in the 26Hz variable runs ( $r = .7, p < 10^{-5}$ ), and in the 30Hz variable run ( $r = .6, p < 10^{-4}$ ).

In the 30Hz stable runs, 26Hz variable runs, and 30Hz variable run, respectively,  $\gamma$  was equal to 1.2 ( $\pm 0.4$ ), to 1.1 ( $\pm 0.3$ ), and to 1.1 ( $\pm 0.2$ ) in the NT group, and to 1.2 ( $\pm 0.5$ ), to 1.0 ( $\pm 0.3$ ), and to 1.3 ( $\pm 0.5$ ) in the ASD group. The ANOVA analysis of the factor group and run (3 kinds of run) on  $\gamma$  revealed no group effect, a run effect ( $F(2,74) = 3.4, p < .05$ ), and no interaction between group and run. Within the ASD group,  $\gamma$  was higher in the 30Hz variable run than in the 26Hz variable run ( $p < .05$ ).  $\gamma$  was positively correlated with  $I_{TOE}$  in the 30Hz stable runs ( $r = .6, p < 10^{-5}$ ), in the 26Hz variable runs ( $r = .7, p < 10^{-6}$ ), and in the 30Hz variable run ( $r = .7, p < 10^{-5}$ ). Additionally,  $\gamma$  was positively correlated with the flexibility parameter in the 30Hz stable runs in the NT group only ( $r = .5, p < .05$ ).

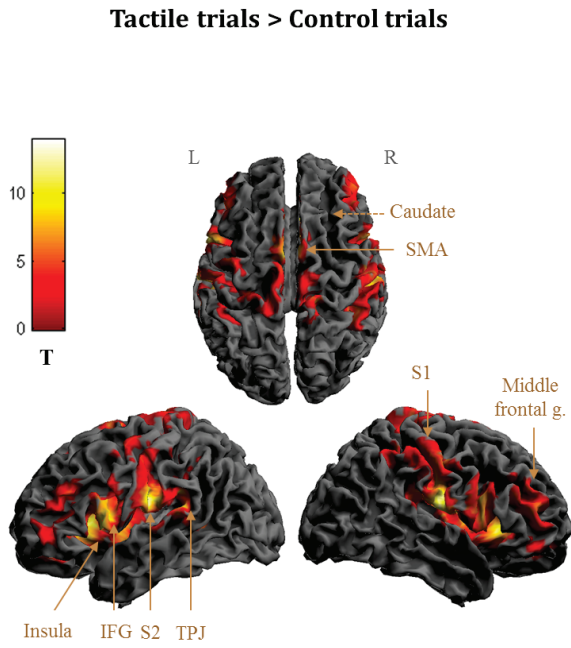
## ***fMRI results***

### ***Trial type analysis***

#### ***Tactile trials vs control trials***

Figure 4 shows the activation pattern for the contrast tactile trial versus control trials in all participants. With  $p < .05$  FWE corrected, the tactile trials elicited increased activity in the contralateral S1, in the bilateral S2, precentral gyri, anterior insula, caudate nucleus, IFG, middle frontal gyri, cerebellum, in the right median cingulate gyrus, inferior parietal gyrus, and in the left orbital part of the superior frontal gyrus, temporo-parietal junction, the supramarginal gyrus and the midbrain (cluster close to substantia nigra).

The NT group showed no cluster with greater activity than the ASD group. For the contrast [tactile trials > control trials], the ASD group showed stronger activity in the left middle occipital gyrus than the NT group ( $T=4.3, x=-28, y=-78, z=40$ ).



Cluster size	Anatomical region	MNI coordinates			T
		x	y	z	
103	R Precentral g.	16	-32	66	8,2
	R Postcentral g. (S1)	16	-40	64	6,5
25	R Postcentral g. (S1)	56	-22	50	6,4
569	L Postcentral g. (S2)	-58	-20	18	12,8
17	L Postcentral g.	-56	-16	46	6,5
18	L Precentral g.	-44	-4	56	6,2
3115	R Rolandic/Postcentral g. (S2)	56	-16	14	11,8
	R Insula, anterior	34	20	2	11,4
	R Caudate nucleus	16	16	0	11,2
2310	L Insula, anterior	-32	18	4	11,3
	L IFG <i>opercularis</i>	-54	10	4	10,9
	L Caudate nucleus	-12	16	-2	9,4
162	R IFG <i>triangularis</i>	46	38	24	7,3
	R Middle frontal g.	44	46	14	6,7
21	L Middle frontal g.	-46	32	28	6,3
14	L Superior frontal g., <i>orbital</i>	-18	42	-14	6,9
1775	R Supplementary motor area	2	16	50	13,9
	L Supplementary motor area	-2	10	56	10,7
	R Median cingulate g.	8	26	32	8,5
182	L Temporo-parietal junction	-54	-40	16	8,9
	L Supramarginal g.	-44	-38	32	6,2
108	R Inferior parietal g.	42	-40	44	7,6
1206	L Cerebellum	-24	-68	-24	10,0
586	R Cerebellum	40	-62	-30	12,0
33	L Midbrain	-10	-18	-14	6,8

**Figure 4: Neural correlates of tactile trials, as compared to control trials**

Results from the contrast Tactile trials > Control trials, in an analysis including the two groups and the four fMRI runs. The significance threshold was set at  $p < .05$  at cluster level and  $p < .001$  at voxel level.

The right table only reports results surviving FWE correction at cluster level.

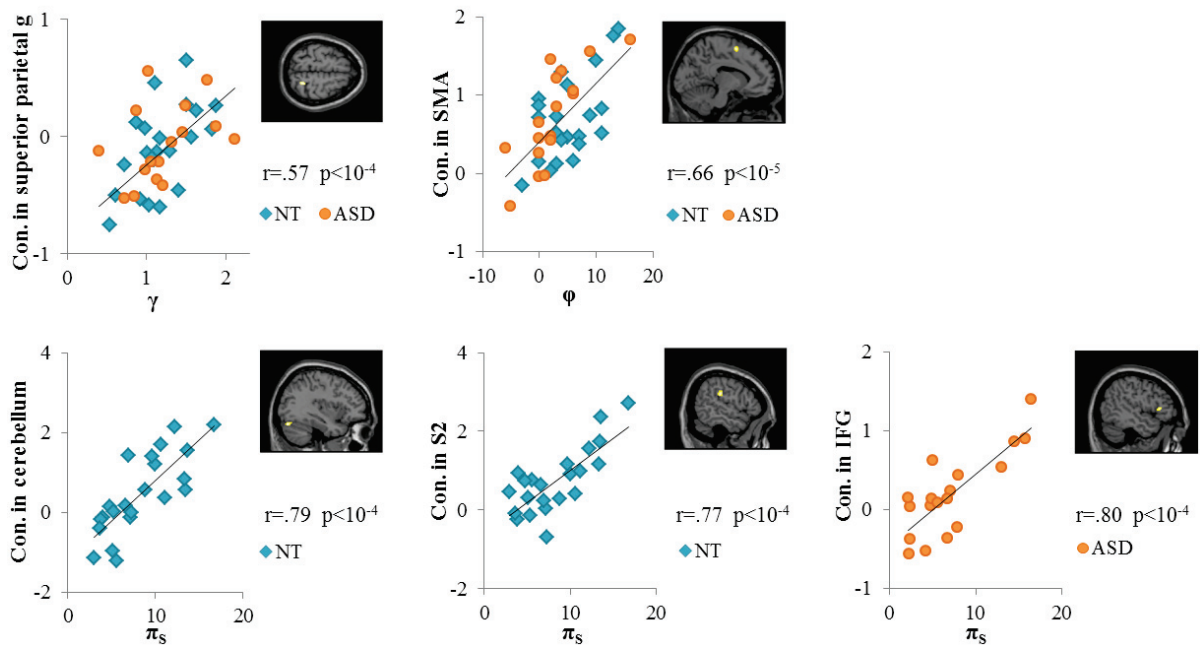
Abbreviations: g: gyrus, IFG: inferior frontal gyrus, TPJ: temporo-parietal junction, SMA: supplementary motor area, S1 and S2: somatosensory cortex I and II.

### Covariate analysis

Results from the covariate analysis are presented in Figure 5. Between participants, increases in the TOE parameter  $\gamma$  were associated with increased activity in the right superior parietal gyrus (2 groups:  $r = .57$ ,  $p < 10^{-4}$ , ASD:  $r = .80$ ,  $p < 10^{-4}$ ). Between NT subjects, increases in precision parameter  $\pi_s$  were associated with increased activity in the left cerebellum ( $r = .79$ ,  $p < 10^{-4}$ ) and right S2 ( $r = .77$ ,  $p < 10^{-4}$ ), and with decreased activity in the right posterior middle temporal gyrus ( $r = -.77$ ,  $p < 10^{-4}$ ). Between ASD subjects, increases in  $\pi_s$  were associated with increased activity in the left IFG *triangularis* ( $r = .80$ ,  $p < 10^{-4}$ ). Between all participants, increases in  $\pi_s$  were associated with decreased activity in the right cuneus and fusiform gyrus. Increases in the flexibility parameter  $\phi$  were associated with increased activity in the left supplementary motor area (2 groups:  $r = .66$ ,  $p < 10^{-5}$ , ASD:  $r = .78$ ,  $p < 10^{-4}$ ). Between ASD participants, increases in the flexibility parameter  $\phi$  were associated with decreased activity in the left fusiform gyrus ( $r = -.89$ ,  $p < 10^{-5}$ ), right middle temporal gyrus ( $r = -.86$ ,  $p < 10^{-5}$ ) and right parahippocampal gyrus ( $r = -.83$ ,  $p < 10^{-4}$ ).



Tactile trials > Control trials									
Covariate	Group		Region		Size	x	y	z	T
$\gamma$	+	2 groups	R	Superior parietal g.	49	22	-54	66	4.4 <sup>#</sup>
	+	ASD	R	Superior parietal g.	44	24	-50	70	5.5
$\pi_s$	+	NT	L	Cerebellum	75	-36	-78	-22	5.6
			R	Supramarginal g. / S2	61	56	-26	28	5.3
	+	ASD	L	IFG, <i>triangularis</i>	38	-48	24	6	5.7
	-	2 groups	R	Cuneus	65	20	-78	44	4.9
$\phi$			R	Fusiform g.	93	38	-68	-14	4.4
	-	NT	R	Middle temporal g. (post.)	55	50	-62	8	5.0
	+	2 groups	L	SMA	69	-10	4	60	5.7
	+	ASD	L	SMA	58	-10	4	60	4.4
	-	ASD	L	Fusiform g.	52	-34	-36	-20	7.4
			R	Middle temporal g. (post.)	82	46	-70	10	6.7
		R	Parahippocampal g.	86	22	-38	-12	5.7	



**Figure 5: Covariate analysis of the model parameters on the contrast [tactile trials > control trials]**  
 The parameters  $\gamma$  (reflecting prior weight on perception),  $\pi_s$  (reflecting sensory precision) and  $\phi$  (reflecting the flexibility to adjust priors) were used as covariates in an analysis including either all participants (“2 groups”), either the NT participants or the ASD participants. Plus and minus signs correspond to positive covariance and negative covariance, respectively. The table presents the results for  $p < .001$  uncorrected level and  $p < .05$  at cluster levels, with results masked by the contrast [tactile trials > control trials]. Coordinates are indicated in the MNI space. The graphics illustrate the correlations involving a positive covariance between the parameters and the contrast estimates. These values of contrast estimates were extracted using Marsbar. # Marginally significant:  $p$ -value at cluster level: .06. IFG: inferior frontal gyrus, S2: secondary somatosensory cortex, g: gyrus, L: left, R: right.

### Functional connectivity

The functional connectivity analysis resulted in a pattern presented in Figure SI-1 (Supplementary information). The time series of all regions were positively correlated with their contralateral equivalent. Times series in S1 were positively correlated with bilateral S2 and bilateral IFG. Additionally, S2 time series were positively correlated with those in

bilateral IFG and ACC, and negatively correlated with those in bilateral IPG. Time series of bilateral IPG were also positively correlated with those in bilateral IFG, while the right IPG was negatively correlated with the left ACC. Group comparison did not reveal any significant difference after Bonferroni correction for multiple comparisons.

### ***Parametric modulator analysis***

#### ***Encoding parametric modulator P1***

Using the encoding parametric modulator P1, we investigated the brain regions whose activity was modulated by the difference between F1 and the frequency prior during the encoding and maintenance periods in the NT and ASD group (Figure 6). The difference between F1 and the prior covaried with the BOLD signal in S1, IFG (*triangularis*, *orbital* and *opercularis*), precentral gyrus, middle frontal gyrus, medial superior frontal gyrus, inferior parietal gyrus, insula, and posterior inferior temporal gyrus in the NT group ( $p < .05$  at cluster level). After FWE correction, P1 modulations in the S1, inferior parietal gyrus, IFG *opercularis*, precentral gyrus, middle frontal gyrus, and medial superior frontal gyrus remained significant in the NT group.

In the ASD group, the regions revealed by the encoding parametric modulator were S1, S2, the supramarginal gyrus, the medial and orbital parts of superior frontal gyrus, the middle frontal gyrus, the IFG (*triangularis* and *opercularis*), the precentral gyrus, the putamen, the inferior parietal gyrus, the temporo-parietal junction, and the anterior insula. After FWE correction, P1 modulation in S2, in the supramarginal gyrus, IFG *opercularis*, middle frontal gyrus, precentral gyrus and putamen remained significant in the ASD group.

The modulation of the activity in the IFG (left orbital part and right triangular part) by the parametric modulator P1 was stronger in the NT group than in the ASD group.

#### ***Covariates analysis (P1)***

The results of the covariate analysis are presented in Table SI-2. Increases in  $\gamma$  were associated with increased modulation of P1 in the left cerebellum between all subjects ( $r = .51, p < .001$ ) and in the left median cingulate gyrus between NT subjects ( $r = .83, p < 10^{-5}$ ). Between ASD subjects, increases in  $\gamma$  were associated with decreased modulation of P1 in the right inferior temporal gyrus ( $r = -.84, p < 10^{-5}$ ), in the right inferior parietal gyrus ( $r = -.76, p < .001$ ), and in the right middle frontal gyrus ( $r = -.74, p < .001$ ). Finally, increases in  $\pi_s$  were associated with decreased modulation of P1 in the right inferior temporal gyrus ( $r = -.65, p < 10^{-5}$ ) and left middle frontal gyrus ( $r = -.60, p < 10^{-4}$ ) between all subjects.

Encoding parametric modulator (p1)						
Cluster size	Anatomical region		MNI coordinates			T
			x	y	z	
NT	921*	R Postcentral g. (S1)	58	-22	48	4,9
		R Inferior parietal g.	52	-36	52	4,6
	74	L Supramarginal g. (S2)	-56	-26	28	3,9
		L Postcentral g. (S2)	-62	-16	22	3,5
	1373*	R Middle frontal g.	44	36	22	6,4
		R IFG opercularis	50	14	28	5,1
	364*	R IFG orbital	40	46	-6	4,1
		R Middle frontal g.	48	50	0	4,1
	585*	L Precentral g / IFG	-54	6	30	6,4
		L IFG opercularis	-54	10	12	6,1
	395*	L IFG triangularis	-48	32	28	5,0
		L Middle frontal g.	-42	48	0	5,0
	508*	R Superior frontal g. medial	4	38	42	4,6
		L Superior frontal g. medial	-6	32	42	4,2
	440*	L Inferior parietal g.	-48	-42	44	5,1
	148	R Insula (ant.)	38	-4	2	4,7
	88	R Insula (ant.)	34	16	-8	4,2
	97	L Insula (ant.)	-32	20	2	4,5
	161	L Insula	-38	-4	10	4,9
	190	R Inferior temporal g. (post.)	60	-50	-16	4,2
137	L Inferior temporal g. (post.)	-54	-38	-14	4,4	
ASD	336*	R Postcentral g. (S2)	62	-14	22	5,2
		R Postcentral g. (S1)	60	-16	42	4,6
	350*	L Rolandic / Postcentral (S2)	-60	-20	26	5,2
	656*	R IFG opercularis	58	14	26	5,9
		R Middle frontal g.	42	36	20	5,3
	447*	L Precentral g. / IFG	-42	4	20	5,1
		L IFG opercularis	-52	8	18	4,4
	144	L Middle frontal g.	-42	42	22	4,0
		L IFG triangularis	-44	30	28	3,4
	200*	L IFG orbital	-38	42	-4	5,2
	144	L Superior frontal g. medial	-6	28	42	4,4
		R Superior frontal g. medial	4	28	46	3,6
	75	R Superior frontal g. orbital	16	18	-20	4,3
		R IFG orbital	28	20	-26	3,2
	96	R Inferior parietal g.	42	-42	50	3,8
	61	L Inferior parietal g.	-50	-52	48	3,3
	105	L Temporo-parietal junction	-52	-42	26	5,3
114	R Insula	34	0	16	4,2	
	R Putamen	34	-6	-2	4,1	
86	L Insula (ant.)	-28	20	-4	4,6	
NT>	75	L IFG orbital	-24	10	-24	4,2
ASD	51 <sup>#</sup>	R IFG triangularis	52	34	4	4,3

**Figure 6: Neural correlates of the Encoding parametric modulator**

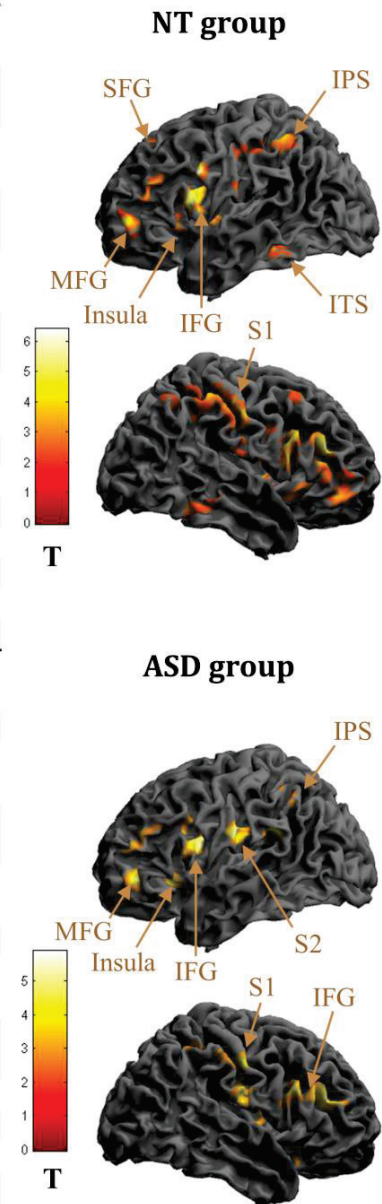
The parametric modulator  $p1$  reflects the integration of F1 sensory information with the prior (average frequency). Results are presented for  $p < .05$  at cluster level (and  $p < .001$  at voxel level). Clusters remaining significant after FWE correction are indicated with a star after cluster size.

NT>ASD: Regions with greater activation in the NT than in the ASD group (<sup>#</sup> marginally significant:  $p = .07$  at cluster level).

No significant cluster was revealed for the comparison ASD>NT.

Hemispheres: L = Left, R = Right.

Abbreviations: g: gyrus, ant: anterior part, post: posterior part, IFG: inferior frontal gyrus.

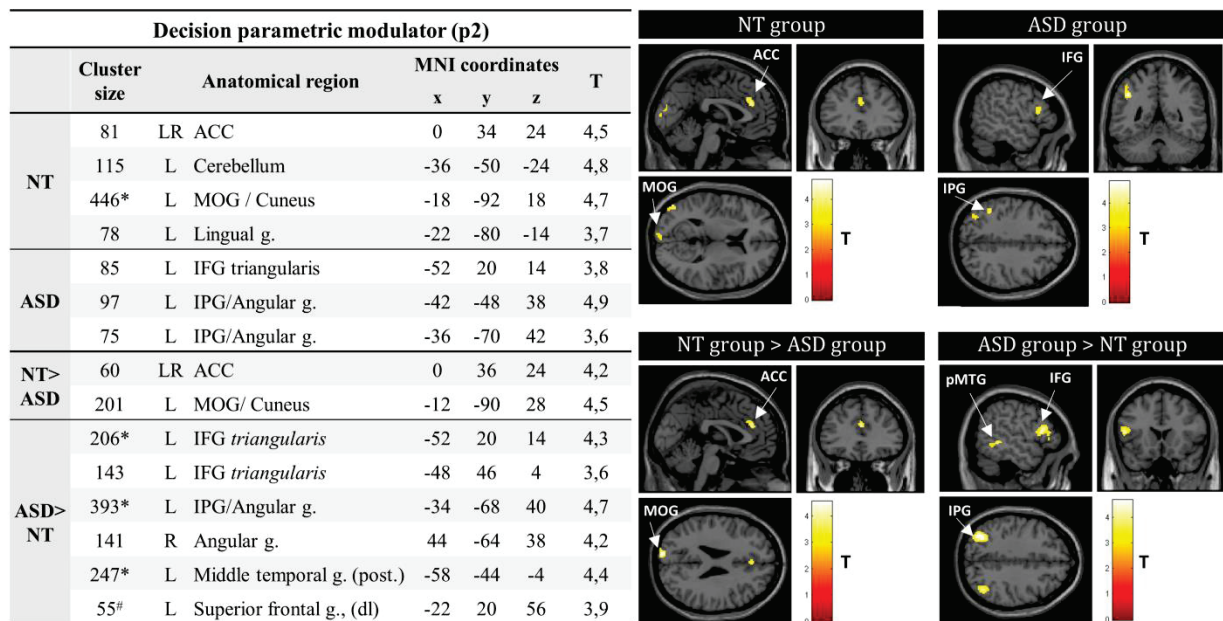


### Comparison parametric regressor P2

Using the comparison parametric modulator P2, we investigated the brain regions whose activity was modulated by subjective difficulty due to the TOE during the comparison of the two frequencies (Figure 7).

The brain regions showing a parametric modulation of the BOLD signal depending of P2 were the ACC, the cerebellum, and the middle occipital gyrus in the NT group. In the ASD group, the brain regions showing a parametric modulation depending of P2 were the inferior parietal gyrus and the IFG (*triangularis*).

The group comparison revealed that the P2 parametric modulation was stronger in the ACC, and superior occipital gyrus in the NT group than in the ASD group. The P2 parametric modulation was stronger in the inferior parietal gyrus, angular gyrus, IFG (*triangularis*), and posterior middle temporal gyrus (pMTG) in the ASD group than in the NT group. In the group comparison, the difference of modulation remaining significant after FWE correction were the stronger modulation in the left inferior parietal gyrus and pMTG in the ASD group than in the NT group.



**Figure 7: Neural correlates of the decision parametric modulator P2**

The parametric modulator P2 reflects the subjective difficulty due to the time-order effect biasing the percept of F1. Results are presented for  $p < .05$  at cluster level (and  $p < .001$  at voxel level). Clusters remaining significant after FWE correction are indicated with a star after cluster size.

NT>ASD: Regions with greater activation in the NT than in the ASD group.

ASD>NT: Regions with greater activation in the ASD than in the NT group.

Hemispheres: L = Left, R = Right. Abbreviations: g: gyrus, s: sulcus, ant: anterior part, post: posterior part, IFG: inferior frontal gyrus, IPG: inferior parietal gyrus, ACC: anterior cingulate cortex, MOG: middle occipital gyrus, SOG: superior occipital gyrus.

***Covariate analysis (P2)***

The results of the covariate analysis are presented in Table SI-2. Between NT subjects, increases in  $\gamma$  were associated with decreased modulation of P2 in the left precuneus ( $r = -.74$ ,  $p < 10^{-4}$ ) and right postcentral gyrus ( $r = -.79$ ,  $p < 10^{-5}$ ).

Between subjects, increases in  $\pi_s$  were associated with increased modulation of P2 in the right cerebellum ( $r = .60$ ,  $p < 10^{-4}$ ), and in large clusters of the parietal lobe between ASD subjects: bilateral supramarginal gyrus (right:  $r = .82$ ,  $p < 10^{-4}$ , left:  $r = .80$ ,  $p < 10^{-4}$ ), bilateral inferior parietal gyrus (right:  $r = .80$ ,  $p < 10^{-4}$ , left:  $r = .77$ ,  $p < .001$ ), and right precuneus ( $r = .78$ ,  $p < 10^{-4}$ ). Between ASD subjects, it was also associated with increased effect of P2 in the right middle frontal gyrus ( $r = .70$ ,  $p < .001$ ) and right SMA ( $r = .72$ ,  $p < .001$ ). Increases in  $\pi_s$  were associated with decreased effect of P2 in the activity of the left dorsolateral part of the superior frontal gyrus in the two groups ( $r = -.61$ ,  $p < 10^{-4}$ ) and in the NT group ( $r = -.77$ ,  $p < 10^{-4}$ ), in the right middle frontal gyrus ( $r = -.74$ ,  $p < 10^{-4}$ ) and right insula ( $r = -.75$ ,  $p < 10^{-5}$ ) in the NT group, and in the left postcentral gyrus ( $r = -.86$ ,  $p < 10^{-4}$ ) and left middle temporal gyrus ( $r = -.80$ ,  $p < 10^{-4}$ ) in the ASD group.

***Parametric regressors in unstable vs. stable runs***

We investigated how the parametric modulators P1 and P2 were influenced by the instability of the context by contrasting the unstable runs (3 and 4) to the stable runs (1 and 2). Note that this contrast must be interpreted cautiously as the order of the unstable and stable runs was not counter-balanced between groups, so that the instability of the context might not be the only one factor influencing these results.

In the unstable context versus stable context, there was a greater modulation by P1 in the left cerebellum ( $T = 4.5$ ,  $-6/-50/-30$ ) and orbital inferior frontal gyrus ( $T = 3.8$ ,  $-36/38/-12$ ) in the NT group. No significant differences were found in the ASD group.

In the unstable context versus stable context, there was a greater modulation by P2: in the right orbital and dorsolateral parts of superior frontal gyrus ( $T = 4.2$ ,  $16/52/-2$ ) in the NT group; and in a cluster covering the left supplementary motor area and medial superior frontal gyrus ( $T=4.1$ ,  $0/12/48$ ) in the ASD group.

## *Discussion*

The present study investigated perception within the Bayesian framework in autism spectrum disorder at the behavioral and neural levels. Using a tactile discrimination task designed to elicit a time-order effect, we explored how prior knowledge biased perception and modulated neural activity. We first confirmed that both NT and ASD subjects were able to implicitly learn priors, and that subjects with ASD had difficulties adjusting their prior in changing contexts. Second, we characterized the brain network involved in the tactile discrimination task, and investigated how it was modulated inter-individually by the size of the TOE and by the precision of the sensory information. Third, we replicated the results by Preuschhof and colleagues on the fMRI parametric modulations in NT (Preuschhof et al. 2010). Fourth, we identified the brain regions whose activities were modulated by two parametric modulators in each group. Indeed, we studied how the difference between the sensory stimulus and the prior during the encoding and maintenance phases covaried with neural activity. We also studied how prior influence on perceptual decision modulated neural activity.

Both the NT and ASD groups showed a TOE, revealed by changes in accuracy depending on the order of presentation of the two frequencies and on the distance between stimulus and prior frequencies. In two previous behavioral studies, we had evidenced a TOE in ASD but occurring after a long and very stable learning phase. In the current study, the familiarization phase was shorter and performed 30 minutes before the TOE task (against 2 minutes before the TOE tasks in the previous experiments). In this context, the ASD group was able to build up a prior, as shown by the TOE. In a changing context, the NT group quickly adapted their prior to the new range of frequencies, contrary to the ASD group who did not show a clear shift in prior frequency. This result confirms that individuals with ASD have difficulties adjusting their priors in a changing context. Such a decreased ability to adjust priors could explain the flexibility difficulties encountered in ASD (Ciesielski and Harris 1997; D’Cruz et al. 2013; Gomot and Wicker 2012; Robertson et al. 2013, 2016; Robic et al. 2014). Inappropriate priors could also lead to enhanced prediction errors (Van de Cruys et al. 2014). The TOE shows that perceptual decisions require short-term memory (about the current tactile stimulus) but also sensory-context integration about the previously delivered stimuli.

We first identified a network involved in the tactile discrimination process, including clusters in the primary and secondary somatosensory cortices, the precentral gyrus, the anterior insula, the caudate nucleus, the IFG, the middle frontal gyrus, orbitofrontal cortex, the SMA, the median cingulate cortex, the inferior and posterior parietal lobules, the temporo-parietal junction and the cerebellum. Previous studies using tactile discrimination tasks in humans showed a very similar neural network (Pleger et al. 2006; Preuschhof et al. 2006). The network we identified included regions like S1 and S2, involve in the encoding of sensory stimuli (see Romo and de Lafuente 2013, for a review), the IFG and IPS important for prior and posterior encoding during maintenance (Aukstulewicz et al. 2011; Preuschhof et al. 2010; Sherman et al. 2016; Spitzer et al. 2010), and the precentral gyrus, SMA, cingulate cortex and superior frontal gyrus important for the decision process (Herding et al. 2016; Preuschhof et al. 2006; Romo and de Lafuente 2013). The two groups did not show any differences in their brain activation pattern for tactile discrimination processes, apart from a cluster in the occipital lobe in ASD. Likewise, the global functional connectivity patterns during tactile trials did not show any group differences. Given the similar patterns of activation for the tactile discrimination task, we were interested in knowing how prediction errors and priors could differently modulate neural activity.

Increases in sensory sensation precision, modeled by  $\pi_S$ , modulated brain activity differently in NT and ASD participants. In NT subjects, high sensory precision  $\pi_S$  was reflected by increased activity in the right secondary somatosensory cortex and in the cerebellum. These regions are implicated in somatosensory perception, and the cerebellum has been associated to prediction error encoding (Bastian 2006; Courchesne and Allen 1997; Gao et al. 1996; Proville et al. 2014; Schlerf et al. 2012; Sinha et al. 2014; Tseng et al. 2007). In another fMRI study, cerebellum activity was modulated by precision weighted prediction errors (Iglesias et al. 2013). Besides, the cerebellum would be implicated in the temporal processing of tactile stimuli (Tinazzi et al. 2013) and in rhythm encoding (Konoike et al. 2012). In contrast, the ASD group showed an association between high sensory precision and high activation level in the left IFG, a region important for somatosensory memory, and high-level prior encoding (Aukstulewicz et al. 2011). Moreover, the increased flexible adjustment of priors, modeled by  $\phi$ , was associated with increased activation in the supplementary motor area (SMA) inter-individually. The SMA was previously found in tactile discrimination tasks, particularly for its involvement for perceptual decisions (Herding et al. 2016; Hernández et al. 2002, 2010; Romo and de Lafuente 2013).

Most importantly, we were interested in determining whether the neural network involved in the tactile discrimination task was modulated by prior information differently in the ASD group as compared to the NT group. First of all, the analysis using the parametric modulator P1 showed that the prediction error on the first stimulation modulated brain activity in the somatosensory cortices, inferior parietal regions, prefrontal regions (including IFG), insula and posterior inferior temporal gyrus in both groups. Noticeably, this network is consistent with the findings by Preuschhof et al. (2010) showing that the prediction error on the first stimulus modulated the activity of somatosensory regions, IFG and inferior parietal lobe. This network modulated by P1 was very close to the one revealed in the contrast between tactile and control discrimination trials. The fact that the activity in S1 and S2 were modulated by P1 suggests that prior information is combined with sensory evidence in early steps of sensory perception, suggesting that prediction errors pass along several levels of cortical hierarchy. The group comparison revealed a greater modulation of the IFG activity by P1 in NT than in ASD. We could expect prediction errors to be given a higher weight when the received frequency is far from the mean of the prior distribution. The decreased modulation by P1 in the IFG in the ASD group could be interpreted as a reduced modulation of the precision of the prediction error during the encoding and maintenance phase in the IFG. This interpretation would be in line with the idea of an inflexible precision of the prediction error in ASD. However, it is important to notice that many brain regions had their activity flexibly adjusted by the size of the prediction error in both groups. Hence, we can hypothesize that the inflexibility of the adjustment of the prediction error weight in ASD could occur mostly for unpredicted changes, rather than for slightly deviant stimuli.

We further investigated how the subjective difficulty in the perceptual decision modulated neural activity. This subjective difficulty is reflected by the TOE where accuracy can be 90% or 40% of correct answers depending on the order of presentation of the stimuli, despite a 2Hz difference in frequency in both cases. The parametric modulator P2 represented this subjective difficulty due to the prior information, and we expected that it would modulate the ACC in controls, like Preuschhof et al. (2010). During the decision phase, increased subjective difficulty (P2) was associated with increased activity in the ACC, cerebellum, and occipital lobe in NT. In ASD, increased difficulty was associated with increased activity in the inferior frontal and parietal gyri. The ACC plays a role in decision-making under uncertainty (Berns et al. 1997; Schultz and Dickinson 2000), as well as prediction error encoding. Interestingly, these four regions were also identified as being modulated by prior precision (Vilares et al. 2012) and precision-weighted prediction errors (Iglesias et al. 2013).



The ACC and cerebellum found in the NT group have been particularly related to prediction errors, and the ACC to uncertainty processing. Indeed, the ACC plays a key role in decision-making under uncertainty and in prediction error encoding (Behrens et al. 2007; Berns et al. 1997; Ide et al. 2013; Schultz and Dickinson 2000). The cerebellum is also involved in the encoding of sensory prediction error (Courchesne and Allen 1997; Dreher and Grafman 2002; Synofzik et al. 2008). The group comparison revealed a greater modulation of the activity of the ACC in NT, but not of the cerebellum. This result could indicate a greater treatment of uncertainty in the decision process of NT subjects.

In ASD, a different pattern involving prefrontal and inferior parietal regions was found. These regions were associated with contextual processing (Barcelo and Knight 2007; Gomot and Wicker 2012; Huettel 2005). Precisely, the IFG would be involved in the encoding of high-level prior (Barredo et al. 2016; Preuschhof et al. 2010; Sanchez 2014.; Spitzer et al. 2010) and/or posterior (d’Acremont et al. 2013; De Martino et al. 2013; Sherman et al. 2016). We found that the modulation of neural activity in prefrontal and inferior parietal regions by the subjective difficulty was greater in the ASD group than in the NT group. Interestingly, in a MMN study, Gomot et al. (2008) found that novelty detection was associated with a stronger activation of the inferior parietal and prefrontal cortices in ASD. Precisely, we found that subjective difficulty increased activity of the IFG, inferior parietal lobe, angular gyrus, posterior middle temporal gyrus and superior frontal gyrus to a greater extent in ASD than NT. Remarkably, this network reminds us of a recent study showing that increased precision of the prediction error leads to greater activity in the IFG, inferior parietal lobe, angular gyrus, posterior middle temporal gyrus, superior medial frontal gyrus and middle orbital gyrus (Sherman et al. 2016).

To conclude, the overall results support the idea that the influence of priors on perceptual decisions and on brain activity differs in ASD. We found a reduced flexibility in the adjustment of prior information in ASD. To fully interpret the behavioral and neuroimaging results in the predictive coding framework, further analyses are needed. Indeed, dynamic causal modeling and the use of computational models capturing the dynamic of prior adjustment and prediction error precision could inform us about a potential high and inflexible precision of the prediction error in ASD. The details of the additional analyses are presented in the perspective section of the general discussion.

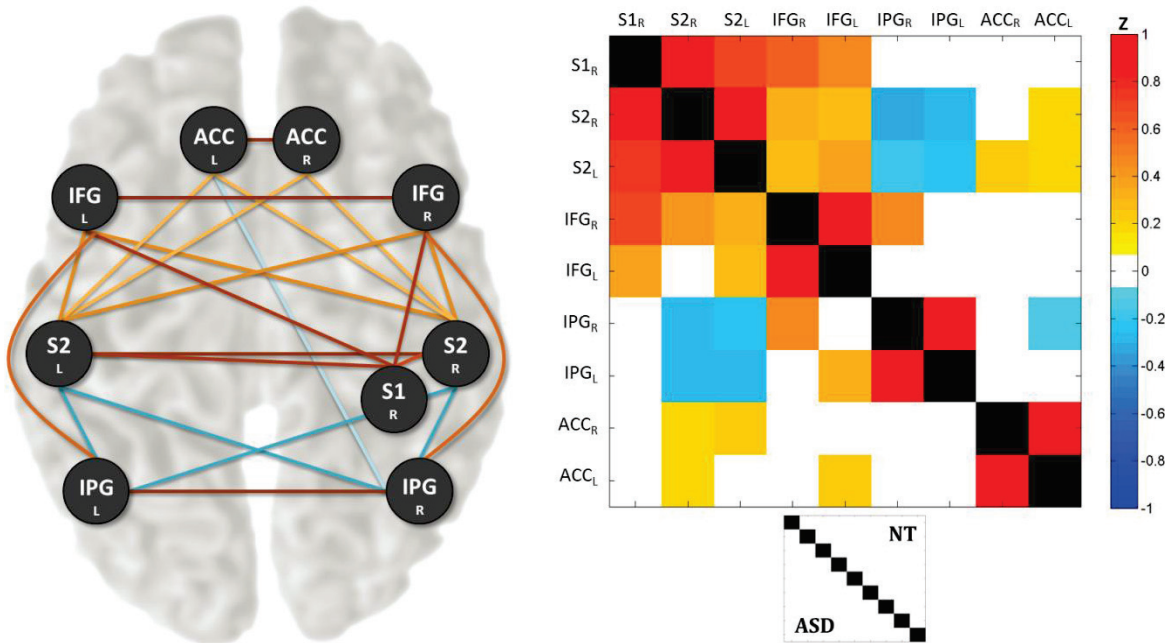
## References

- American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders*. American Psychiatric Association.
- Ashourian, P., & Loewenstein, Y. (2011). Bayesian inference underlies the contraction bias in delayed comparison tasks. *PLoS one*, 6(5), e19551. doi:10.1371/journal.pone.0019551
- Auksztulewicz, R., Spitzer, B., Goltz, D., & Blankenburg, F. (2011). Impairing somatosensory working memory using rTMS. *The European Journal of Neuroscience*, 34(5), 839–844. doi:10.1111/j.1460-9568.2011.07797.x
- Barcelo, F., & Knight, R. T. (2007). An information-theoretical approach to contextual processing in the human brain: evidence from prefrontal lesions. *Cerebral Cortex (New York, N.Y.: 1991)*, 17 Suppl 1, i51-60. doi:10.1093/cercor/bhm111
- Baron-Cohen, S., Wheelwright, S., Robinson, J., & Woodbury-Smith, M. (2005). The Adult Asperger Assessment (AAA): a diagnostic method. *Journal of Autism and Developmental Disorders*, 35(6), 807–819. doi:10.1007/s10803-005-0026-5
- Barredo, J., Verstynen, T. D., & Badre, D. (2016). Organization of cortico-cortical pathways supporting memory retrieval across subregions of the left ventrolateral prefrontal cortex. *Journal of Neurophysiology*, 116(3), 920–937. doi:10.1152/jn.00157.2016
- Bastian, A. J. (2006). Learning to predict the future: the cerebellum adapts feedforward movement control. *Current Opinion in Neurobiology*, 16(6), 645–649. doi:10.1016/j.conb.2006.08.016
- Behrens, T. E. J., Woolrich, M. W., Walton, M. E., & Rushworth, M. F. S. (2007). Learning the value of information in an uncertain world. *Nature Neuroscience*, 10(9), 1214–1221. doi:10.1038/nn1954
- Behzadi, Y., Restom, K., Liu, J., & Liu, T. T. (2007). A component based noise correction method (CompCor) for BOLD and perfusion based fMRI. *NeuroImage*, 37(1), 90–101. doi:10.1016/j.neuroimage.2007.04.042
- Berns, G. S., Cohen, J. D., & Mintun, M. A. (1997). Brain regions responsive to novelty in the absence of awareness. *Science (New York, N.Y.)*, 276(5316), 1272–1275.
- Brock, J. (2012). Alternative Bayesian accounts of autistic perception: comment on Pellicano and Burr. *Trends in Cognitive Sciences*, 16(12), 573–574. doi:10.1016/j.tics.2012.10.005
- Brody, C. D., Hernández, A., Zainos, A., Lemus, L., & Romo, R. (2002). Analysing neuronal correlates of the comparison of two sequentially presented sensory stimuli. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 357(1428), 1843–1850. doi:10.1098/rstb.2002.1167
- Camarillo, L., Luna, R., Nácher, V., & Romo, R. (2012). Coding perceptual discrimination in the somatosensory thalamus. *Proceedings of the National Academy of Sciences of the United States of America*, 109(51), 21093–21098. doi:10.1073/pnas.1219636110
- Christensen, D. L., Baio, J., Van Naarden Braun, K., Bilder, D., Charles, J., Constantino, J. N., et al. (2016). Prevalence and Characteristics of Autism Spectrum Disorder Among Children Aged 8 Years--Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2012. *Morbidity and Mortality Weekly Report. Surveillance Summaries (Washington, D.C.: 2002)*, 65(3), 1–23. doi:10.15585/mmwr.ss6503a1
- Ciesielski, K. T., & Harris, R. J. (1997). Factors related to performance failure on executive tasks in autism. *Child Neuropsychology*, 3(1), 1–12. doi:10.1080/09297049708401364
- Courchesne, E., & Allen, G. (1997). Prediction and preparation, fundamental functions of the cerebellum. *Learning & Memory (Cold Spring Harbor, N.Y.)*, 4(1), 1–35.
- d’Acemont, M., Schultz, W., & Bossaerts, P. (2013). The Human Brain Encodes Event Frequencies While Forming Subjective Beliefs. *The Journal of neuroscience: the official journal of the Society for Neuroscience*, 33(26), 10887. doi:10.1523/JNEUROSCI.5829-12.2013
- D’Cruz, A.-M., Ragozzino, M. E., Mosconi, M. W., Shrestha, S., Cook, E. H., & Sweeney, J. A. (2013). Reduced behavioral flexibility in autism spectrum disorders. *Neuropsychology*, 27(2), 152–160. doi:10.1037/a0031721
- De Martino, B., Fleming, S. M., Garrett, N., & Dolan, R. J. (2013). Confidence in value-based choice. *Nature Neuroscience*, 16(1), 105–110. doi:10.1038/nn.3279
- Dodel, S., Golestani, N., Pallier, C., Elkouby, V., Le Bihan, D., & Poline, J.-B. (2005). Condition-dependent functional connectivity: syntax networks in bilinguals. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, 360(1457), 921–935. doi:10.1098/rstb.2005.1653
- Dreher, J.-C., & Grafman, J. (2002). The roles of the cerebellum and basal ganglia in timing and error prediction: Cerebellar and striatal functions in timing and error prediction. *European Journal of Neuroscience*, 16(8), 1609–1619. doi:10.1046/j.1460-9568.2002.02212.x
- Friston, K. J., Harrison, L., & Penny, W. (2003). Dynamic causal modelling. *NeuroImage*, 19(4), 1273–1302.
- Gao, J. H., Parsons, L. M., Bower, J. M., Xiong, J., Li, J., & Fox, P. T. (1996). Cerebellum implicated in sensory acquisition and discrimination rather than motor control. *Science (New York, N.Y.)*, 272(5261), 545–547.

- García-Pérez, M. A. (1998). Forced-choice staircases with fixed step sizes: asymptotic and small-sample properties. *Vision Research*, 38(12), 1861–1881.
- Gomot, M., Belmonte, M. K., Bullmore, E. T., Bernard, F. A., & Baron-Cohen, S. (2008). Brain hyper-reactivity to auditory novel targets in children with high-functioning autism. *Brain*, 131(9), 2479–2488. doi:10.1093/brain/awn172
- Gomot, M., & Wicker, B. (2012). A challenging, unpredictable world for people with autism spectrum disorder. *International journal of psychophysiology: official journal of the International Organization of Psychophysiology*, 83(2), 240–247. doi:10.1016/j.ijpsycho.2011.09.017
- Gorgolewski, K., Burns, C. D., Madison, C., Clark, D., Halchenko, Y. O., Waskom, M. L., & Ghosh, S. S. (2011). Nipype: a flexible, lightweight and extensible neuroimaging data processing framework in Python. *Frontiers in Neuroinformatics*, 5, 13. doi:10.3389/fninf.2011.00013
- Harris, J. A., Arabzadeh, E., Fairhall, A. L., Benito, C., & Diamond, M. E. (2006). Factors Affecting Frequency Discrimination of Vibrotactile Stimuli: Implications for Cortical Encoding. *PLoS ONE*, 1(1). doi:10.1371/journal.pone.0000100
- Harris, J. A., Miniussi, C., Harris, I. M., & Diamond, M. E. (2002). Transient Storage of a Tactile Memory Trace in Primary Somatosensory Cortex. *Journal of Neuroscience*, 22(19), 8720–8725.
- Herding, J., Spitzer, B., & Blankenburg, F. (2016). Upper Beta Band Oscillations in Human Premotor Cortex Encode Subjective Choices in a Vibrotactile Comparison Task. *Journal of Cognitive Neuroscience*, 28(5), 668–679. doi:10.1162/jocn\_a\_00932
- Hernández, A., Salinas, E., García, R., & Romo, R. (1997). Discrimination in the sense of flutter: new psychophysical measurements in monkeys. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, 17(16), 6391–6400.
- Hernández, Adrián, Nácher, V., Luna, R., Zainos, A., Lemus, L., Alvarez, M., et al. (2010). Decoding a perceptual decision process across cortex. *Neuron*, 66(2), 300–314. doi:10.1016/j.neuron.2010.03.031
- Hernández, Adrián, Zainos, A., & Romo, R. (2000). Neuronal correlates of sensory discrimination in the somatosensory cortex. *Proceedings of the National Academy of Sciences of the United States of America*, 97(11), 6191–6196.
- Hernández, Adrián, Zainos, A., & Romo, R. (2002). Temporal Evolution of a Decision-Making Process in Medial Premotor Cortex. *Neuron*, 33(6), 959–972. doi:10.1016/S0896-6273(02)00613-X
- Hollingworth, H. L. (1910). The Central Tendency of Judgment. *The Journal of Philosophy, Psychology and Scientific Methods*, 7(17), 461–469. doi:10.2307/2012819
- Huettel, S. A. (2005). Decisions under Uncertainty: Probabilistic Context Influences Activation of Prefrontal and Parietal Cortices. *Journal of Neuroscience*, 25(13), 3304–3311. doi:10.1523/JNEUROSCI.5070-04.2005
- Ide, J. S., Shenoy, P., Yu, A. J., & Li, C. R. (2013). Bayesian prediction and evaluation in the anterior cingulate cortex. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, 33(5), 2039–2047. doi:10.1523/JNEUROSCI.2201-12.2013
- Iglesias, S., Mathys, C., Brodersen, K. H., Kasper, L., Piccirelli, M., den Ouden, H. E. M., & Stephan, K. E. (2013). Hierarchical prediction errors in midbrain and basal forebrain during sensory learning. *Neuron*, 80(2), 519–530. doi:10.1016/j.neuron.2013.09.009
- Kalberlah, C., Villringer, A., & Pleger, B. (2013). Dynamic causal modeling suggests serial processing of tactile vibratory stimuli in the human somatosensory cortex--an fMRI study. *NeuroImage*, 74, 164–171. doi:10.1016/j.neuroimage.2013.02.018
- Karim, M., Harris, J. A., Langdon, A., & Breakspear, M. (2013). The influence of prior experience and expected timing on vibrotactile discrimination. *Frontiers in Neuroscience*, 7. doi:10.3389/fnins.2013.00255
- Khan, S., Michmizos, K., Tommerdahl, M., Ganesan, S., Kitzbichler, M. G., Zetino, M., et al. (2015). Somatosensory cortex functional connectivity abnormalities in autism show opposite trends, depending on direction and spatial scale. *Brain*, 138(5), 1394. doi:10.1093/brain/awv043
- Konoike, N., Kotozaki, Y., Miyachi, S., Miyachi, C. M., Yomogida, Y., Akimoto, Y., et al. (2012). Rhythm information represented in the fronto-parieto-cerebellar motor system. *NeuroImage*, 63(1), 328–338. doi:10.1016/j.neuroimage.2012.07.002
- Kostopoulos, P., Albanese, M.-C., & Petrides, M. (2007). Ventrolateral prefrontal cortex and tactile memory disambiguation in the human brain. *Proceedings of the National Academy of Sciences of the United States of America*, 104(24), 10223–10228. doi:10.1073/pnas.0700253104
- Lawson, R. P., Rees, G., & Friston, K. J. (2014). An aberrant precision account of autism. *Frontiers in Human Neuroscience*, 8, 302. doi:10.3389/fnhum.2014.00302
- Lemus, L., Hernández, A., Luna, R., Zainos, A., Nácher, V., & Romo, R. (2007). Neural correlates of a postponed decision report. *Proceedings of the National Academy of Sciences of the United States of America*, 104(43), 17174–17179. doi:10.1073/pnas.0707961104
- Liang, M., Mouraux, A., & Iannetti, G. D. (2011). Parallel processing of nociceptive and non-nociceptive somatosensory information in the human primary and secondary somatosensory cortices: evidence from

- dynamic causal modeling of functional magnetic resonance imaging data. *The Journal of Neuroscience*, 31(24), 8976–8985. doi:10.1523/JNEUROSCI.6207-10.2011
- Lord, C., Risi, S., Lambrecht, L., Cook, E. H., Leventhal, B. L., DiLavore, P. C., et al. (2000). The autism diagnostic observation schedule-generic: a standard measure of social and communication deficits associated with the spectrum of autism. *Journal of Autism and Developmental Disorders*, 30(3), 205–223.
- Lord, C., Rutter, M., & Le Couteur, A. (1994). Autism Diagnostic Interview-Revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *Journal of Autism and Developmental Disorders*, 24(5), 659–685.
- Luna, R., Hernández, A., Brody, C. D., & Romo, R. (2005). Neural codes for perceptual discrimination in primary somatosensory cortex. *Nature Neuroscience*, 8(9), 1210–1219. doi:10.1038/nn1513
- Mathys, C. D., Lomakina, E. I., Daunizeau, J., Iglesias, S., Brodersen, K. H., Friston, K. J., & Stephan, K. E. (2014). Uncertainty in perception and the Hierarchical Gaussian Filter. *Frontiers in Human Neuroscience*, 8. doi:10.3389/fnhum.2014.00825
- Mountcastle, V. B., Steinmetz, M. A., & Romo, R. (1990). Frequency discrimination in the sense of flutter: psychophysical measurements correlated with postcentral events in behaving monkeys. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, 10(9), 3032–3044.
- Palmer, C. J., Lawson, R. P., & Hohwy, J. (2017). Bayesian Approaches to Autism: Towards Volatility, Action, and Behavior. *Psychological Bulletin*. doi:10.1037/bul0000097
- Pellicano, E., & Burr, D. (2012). When the world becomes “too real”: a Bayesian explanation of autistic perception. *Trends in cognitive sciences*, 16(10), 504–510. doi:10.1016/j.tics.2012.08.009
- Pleger, B., Ruff, C. C., Blankenburg, F., Bestmann, S., Wiech, K., Stephan, K. E., et al. (2006). Neural Coding of Tactile Decisions in the Human Prefrontal Cortex. *Journal of Neuroscience*, 26(48), 12596–12601. doi:10.1523/JNEUROSCI.4275-06.2006
- Pleger, B., & Villringer, A. (2013). The human somatosensory system: From perception to decision making. *Progress in Neurobiology*, 103, 76–97. doi:10.1016/j.pneurobio.2012.10.002
- Preuschhof, C., Heekeren, H. R., Taskin, B., Schubert, T., & Villringer, A. (2006). Neural correlates of vibrotactile working memory in the human brain. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, 26(51), 13231–13239. doi:10.1523/JNEUROSCI.2767-06.2006
- Preuschhof, C., Schubert, T., Villringer, A., & Heekeren, H. R. (2010). Prior Information biases stimulus representations during vibrotactile decision making. *Journal of Cognitive Neuroscience*, 22(5), 875–887. doi:10.1162/jocn.2009.21260
- Proville, R. D., Spolidoro, M., Guyon, N., Dugué, G. P., Selimi, F., Isope, P., et al. (2014). Cerebellum involvement in cortical sensorimotor circuits for the control of voluntary movements. *Nature Neuroscience*, 17(9), 1233–1239. doi:10.1038/nn.3773
- Robertson, C. E., Kravitz, D. J., Freyberg, J., Baron-Cohen, S., & Baker, C. I. (2013). Slower Rate of Binocular Rivalry in Autism. *Journal of Neuroscience*, 33(43), 16983–16991. doi:10.1523/JNEUROSCI.0448-13.2013
- Robertson, Caroline E., Ratai, E.-M., & Kanwisher, N. (2016). Reduced GABAergic Action in the Autistic Brain. *Current Biology*, 26(1), 80–85. doi:10.1016/j.cub.2015.11.019
- Robic, S., Sonié, S., Fonlupt, P., Henaff, M.-A., Touil, N., Coricelli, G., et al. (2014). Decision-Making in a Changing World: A Study in Autism Spectrum Disorders. *Journal of Autism and Developmental Disorders*. doi:10.1007/s10803-014-2311-7
- Romo, R., & de Lafuente, V. (2013). Conversion of sensory signals into perceptual decisions. *Progress in Neurobiology*, 103, 41–75. doi:10.1016/j.pneurobio.2012.03.007
- Romo, R., Hernández, A., Zainos, A., Brody, C. D., & Lemus, L. (2000). Sensing without Touching: Psychophysical Performance Based on Cortical Microstimulation. *Neuron*, 26(1), 273–278. doi:10.1016/S0896-6273(00)81156-3
- Romo, R., Hernández, A., Zainos, A., & Salinas, E. (1998). Somatosensory discrimination based on cortical microstimulation. *Nature*, 392(6674), 387–390. doi:10.1038/32891
- Rossi-Pool, R., Salinas, E., Zainos, A., Alvarez, M., Vergara, J., Parga, N., & Romo, R. (2016). Emergence of an abstract categorical code enabling the discrimination of temporally structured tactile stimuli. *Proceedings of the National Academy of Sciences of the United States of America*, 113(49), E7966–E7975. doi:10.1073/pnas.1618196113
- Salinas, E., Hernandez, A., Zainos, A., & Romo, R. (2000). Periodicity and firing rate as candidate neural codes for the frequency of vibrotactile stimuli. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, 20(14), 5503–5515.
- Sanchez G. (2014). Real-Time Electrophysiology in Cognitive Neuroscience : Towards Adaptive Paradigms to study perceptual Learning and Decision-Making in Humans. PhD thesis, Lyon 1 University, France.

- Schlerf, J., Ivry, R. B., & Diedrichsen, J. (2012). Encoding of sensory prediction errors in the human cerebellum. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, 32(14), 4913–4922. doi:10.1523/JNEUROSCI.4504-11.2012
- Schultz, W., & Dickinson, A. (2000). Neuronal coding of prediction errors. *Annual Review of Neuroscience*, 23, 473–500. doi:10.1146/annurev.neuro.23.1.473
- Sherman, M. T., Seth, A. K., & Kanai, R. (2016). Predictions Shape Confidence in Right Inferior Frontal Gyrus. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, 36(40), 10323–10336. doi:10.1523/JNEUROSCI.1092-16.2016
- Sinclair, R. J., & Burton, H. (1996). Discrimination of vibrotactile frequencies in a delayed pair comparison task. *Perception & Psychophysics*, 58(5), 680–692.
- Sinha, P., Kjelgaard, M. M., Gandhi, T. K., Tsourides, K., Cardinaux, A. L., Pantazis, D., et al. (2014). Autism as a disorder of prediction. *Proceedings of the National Academy of Sciences of the United States of America*, 111(42), 15220–15225. doi:10.1073/pnas.1416797111
- Sörös, P., Marmurek, J., Tam, F., Baker, N., Staines, W. R., & Graham, S. J. (2007). Functional MRI of working memory and selective attention in vibrotactile frequency discrimination. *BMC Neuroscience*, 8(1), 48. doi:10.1186/1471-2202-8-48
- Spitzer, B., Wacker, E., & Blankenburg, F. (2010). Oscillatory correlates of vibrotactile frequency processing in human working memory. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, 30(12), 4496–4502. doi:10.1523/JNEUROSCI.6041-09.2010
- Synofzik, M., Lindner, A., & Thier, P. (2008). The cerebellum updates predictions about the visual consequences of one's behavior. *Current biology: CB*, 18(11), 814–818. doi:10.1016/j.cub.2008.04.071
- Tang, K., Staines, W. R., Black, S. E., & McIlroy, W. E. (2009). Novel vibrotactile discrimination task for investigating the neural correlates of short-term learning with fMRI. *Journal of Neuroscience Methods*, 178(1), 65–74. doi:10.1016/j.jneumeth.2008.11.024
- Tinazzi, M., Morgante, F., Peretti, A., Mariotti, C., Panzeri, M., Fiorio, M., & Fasano, A. (2013). Impaired temporal processing of tactile and proprioceptive stimuli in cerebellar degeneration. *PloS One*, 8(11), e78628. doi:10.1371/journal.pone.0078628
- Tseng, Y.-W., Diedrichsen, J., Krakauer, J. W., Shadmehr, R., & Bastian, A. J. (2007). Sensory prediction errors drive cerebellum-dependent adaptation of reaching. *Journal of Neurophysiology*, 98(1), 54–62. doi:10.1152/jn.00266.2007
- Van de Cruys, S., Evers, K., Van der Hallen, R., Van Eylen, L., Boets, B., de-Wit, L., & Wagemans, J. (2014). Precise minds in uncertain worlds: predictive coding in autism. *Psychological Review*, 121(4), 649–675. doi:10.1037/a0037665
- Vázquez, Y., Salinas, E., & Romo, R. (2013). Transformation of the neural code for tactile detection from thalamus to cortex. *Proceedings of the National Academy of Sciences of the United States of America*, 110(28), E2635–E2644. doi:10.1073/pnas.1309728110
- Vilares, I., Howard, J. D., Fernandes, H. L., Gottfried, J. A., & Kording, K. P. (2012). Differential representations of prior and likelihood uncertainty in the human brain. *Current biology: CB*, 22(18), 1641–1648. doi:10.1016/j.cub.2012.07.010

*Supplementary information***SI-1: Functional connectivity analysis of tactile trials**

The left figure illustrates the functional connectivity pattern of the two groups during tactile trials. Orange to red connections show positive correlations between time series, while blue connections indicate negative correlations. The lighter the color is, the lower the correlation coefficient is. This pattern shows connections which survived FWE correction.

The right figure shows the Z values of the NT (upper diagonal) and ASD groups (lower diagonal). The bar color was staked between -1 and 1, but Z scores go up to 1,3. When one-way t-test comparing the Z-score to 0 did not give significant results surviving FWE corrections, the corresponding part of the matrix was colored with white. Group comparison between the NT and ASD group did not give any significant difference after correction for multiple comparisons using Bonferroni.

R: right, L: left, S1 and S2: primary and secondary somatosensory cortices, IFG: inferior frontal gyrus, IPG: inferior parietal gyrus, ACC: anterior cingulate cortex.

Encoding parametric modulator P1									
Covariate	Group	Region	Size	x	y	z	T		
$\gamma$	+	2 groups	L Cerebellum	77	-6	-62	-14	4.4	
			L Median cingulate g.	93	-14	-26	38	4.5	
	-	ASD	R ITG/MTG	207	64	-24	-12	6.5*	
			R IPG/Angular g.	138	50	-48	44	4.7	
			R Middle frontal g.	66	38	14	44	4.3	
$\pi_s$	-	2 groups	R Inferior temporal g.	53	44	-40	-20	5.8	
			L Middle frontal g.	49	-36	46	16	4.3	

Decision parametric modulator P2									
Covariate	Group	Region	Size	x	y	z	T		
$\gamma$	-	NT	L Precuneus	100	-12	-52	50	4.8	
			R Postcentral g.	86	28	-32	36	4.4	
$\pi_s$	+	2 groups	R Cerebellum	87	38	-66	-20	5.1	
			R Supramarginal g.	768	60	-32	40	6.8*	
	+	ASD	L Supramarginal g.	264	-58	-32	24	5.3*	
			R IPG /Superior parietal g.	245	34	-40	38	4.9*	
			L IPG	400	-48	-40	52	5.1*	
			R Precuneus	96	8	-68	54	5.9	
			R Middle frontal g.	78	42	38	30	4.3	
			R SMA	77	2	12	54	4.2	
			-	2 groups	L Superior frontal g., dl	44	-22	-8	62
	-	NT	R Middle frontal g.	136	38	36	18	5.6	
			L Superior frontal g., dl	103	-24	-4	62	5.0	
			R Insula	72	40	16	-14	4.9	
			-	ASD	L Postcentral g.	157	-36	-28	70
		L Middle temporal g.	190	-48	-12	-22	4.9*		

**SI-2: Covariate analysis of the parameters  $\gamma$  and  $\pi_s$  on the parametric modulation by P1 during encoding and P2 during decision**

The table presents the results for  $p < .001$  uncorrected level and  $p < .05$  at cluster levels, with results masked by the contrast [tactile trials > control trials]. Results surviving FWE correction at cluster level are indicated by a star after the T value. Coordinates are indicated in the MNI space. Plus and minus sign indicate positive and negative covariance effects.

ITG/MTG: inferior and middle temporal gyrus, IPG: inferior parietal gyrus, SMA: supplementary motor area, dl: dorsolateral part, R: right, L: left.

## *Magnetic resonance spectroscopy study*

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### Neurobiological underpinning of perceptual inference in ASD

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#### *Introduction*

A challenging aspect in the understanding of autism spectrum disorder is that symptoms would be caused by atypical brain functioning due to complex genetic, environmental and epigenetic interactions. At the molecular level, one of the main hypotheses suggests that autism spectrum disorders (ASD) could arise from an increased excitatory/inhibitory balance (Hussman 2001; Rubenstein and Merzenich 2003; Lam et al. 2006; Yizhar et al. 2011; Rosenberg et al. 2015). This ratio, mostly mediated by glutamate/GABA, is involved in the control of neural noise. In ASD, both increased and decreased neural noises have been suggested (Simmons et al. 2007, 2009; Davis and Plaisted-Grant 2015). The only current non-invasive technique offering the opportunity to measure *in vivo* glutamate and GABA levels is magnetic resonance spectroscopy (MRS) (Edden et al. 2009; Puts et al. 2011, 2016; Puts and Edden 2012). Several MRS studies have shown a decreased GABA concentration in children with ASD: in the prefrontal cortex (Harada et al. 2011), in auditory (Gaetz et al. 2014) and somatosensory regions (Puts et al. 2016). Yet, the only GABA MRS study in adults with ASD showed no differences in GABA levels in the occipital lobe (Robertson et al. 2016). In ASD, an increased glutamate/GABA balance could be due to genetic variations in genes encoding GABA receptors (Shao et al. 2003; Ma et al. 2005; Piton et al. 2013), to a reduced number of GABA receptors (Fatemi et al. 2014), to immature GABA neurons (Ben-Ari et al. 2012), or to a reduced level of GAD enzyme (Glutamate acid decarboxylase, converting glutamate into GABA) (Fatemi et al. 2002). Clinical studies have been testing the effects of bumetanide administration in ASD, a diuretic supposed to help GABAergic neurons to mature and to become inhibitors. Bumetanide administration was associated with reduced autistic symptoms in some of the children with ASD (Lemonnier and Ben-Ari 2010; Lemonnier et al. 2017). Increasing GABA inhibition in mice models of ASD also improved behavioral autistic symptoms (Han et al. 2014). Abnormally high glutamate/GABA ratio could lead to increased neural noise and glutamate excitotoxicity, and abnormal brain development (Bittigau and Ikonomidou 1997; El-Ansary and Al-Ayadhi 2014).



Previous studies have been suggesting that in ASD, an increased Glutamate/GABA balance could explain the atypical sensory sensitivity, but also certain aspects of perceptual inference and learning (Puts et al. 2011; Rosenberg et al. 2015). Perceptual inference corresponds to the process by which we can predict and interpret the incoming sensory inputs based on our prior knowledge. In the Bayesian framework, percepts result from the weighted interplay between sensory inputs and priors. Rosenberg and colleagues developed computational models to explain how GABAergic and glutamatergic neuromodulations could account for autistic symptomatology, particularly in the Bayesian framework (Rosenberg et al. 2015). Precisely, they used models based on divisive normalization, which is a computation that divides the activity of a neuron by the combined activity of the neuronal population in which the neuron is embedded. The suppressive field gain controls the extent to which the neuronal population influences the activity of a neuron. Decreased GABA concentrations would be associated with reduced suppressive field gain. According to their models, the less influence a population has on the activity of individual neurons (i.e. low suppressive field gain), the more severe autistic symptoms are. In addition, their simulations suggest that experience (prior) changes the strength of lateral connectivity across the neuronal population. They also suggest that the plasticity of these connections could be weaker in ASD, reducing the effect of priors. Decreased GABAergic modulation (relatively to glutamatergic transmission) would be associated with a reduced weight of priors on perception. The hypothesis of a decreased suppressive field gain in ASD would be in line with an imbalance in the relative weight of sensory inputs and priors in ASD (Pellicano and Burr 2012; Brock 2012; Lawson et al. 2014; Van de Cruys et al. 2014).

The only study measuring GABA in adults with ASD could also be interpreted within the Bayesian framework (Robertson et al. 2016). In their binocular rivalry task, they measured the percentage of perceptual suppression, which can be seen as attempts to minimize prediction errors in a context of high likelihood and high prior probabilities (Hohwy et al. 2008). They found that the ASD group showed reduced perceptual suppression leading to more mixed percepts, which could be interpreted as a reduced influence of top-down predictions (Van de Cruys et al. 2014). The percentage of perceptual suppression was positively correlated with GABA and glutamate concentrations in controls, and with glutamate concentration only in ASD (Robertson et al. 2016). It suggests that a decreased influence of predictions on perception could be associated with a decreased GABA action in the ASD group (Robertson et al. 2016).

Here, we used MRS to measure glutamate and GABA concentrations in the somatosensory cortices of adults with or without ASD. We first wanted to determine whether adults with ASD had reduced GABA levels in the somatosensory cortex, as children with ASD did. We were further interested in (1) investigating the relationships between sensory sensitivity and glutamate/GABA levels, and (2) in studying whether prior influence on perception could be mediated by GABA modulation.

Sensory sensitivity was assessed by tactile threshold measurements and by the Glasgow Sensory Questionnaire (Robertson and Simmons 2013). We expected lower perceptual thresholds to be associated with lower GABA concentrations and higher glutamate concentrations. High GABA levels could either inhibit the global signal or increase the signal-to-noise ratio. Hence, we could expect higher GABA to be associated either with lower tactile hypersensitivity or with higher precision in threshold measurements and higher tactile hypersensitivity. Besides, we assessed the effect of prior weight on perceptual decisions using the time-order effect presented in the fMRI study. We expected a decreased suppressive field gain (i.e. increased glutamate/GABA ratio) to be associated with a decreased influence of priors on perception (Rosenberg et al. 2015).

## *Material and Methods*

### ***Participants***

The study was performed on twenty-one neurotypical (NT) participants and 20 participants with ASD. Two NT and two ASD subjects were discarded from the analyses as one of their spectra showed signs of lipid contamination. The remaining groups of 19 NT (13 males) and 18 ASD (13 males) participants were matched in age, gender ratio, education level and IQ. Mean age and education levels (in years) were respectively 33.2 ( $\pm 8.4$ ) and 16.0 ( $\pm 2.2$ ) in the NT group and 35.0 ( $\pm 10.2$ ) and 15.5 ( $\pm 2.5$ ) in the ASD group. The two groups were also matched for the total Intellectual Quotient, measured with the WAIS IV (NT: 120  $\pm 11$ , ASD: 125  $\pm 20$ ). All participants presented with no intellectual deficiency and had no history of neurological disorders. The ASD subjects met criteria for ASD without language onset delay according to the Diagnostic and Statistical Manual of Mental Disorders V (American Psychiatric Association 2013), and were diagnosed by a specialized psychiatrist after having undergone the ADI-R (Autism Diagnostic Interview-Revised, Lord et al. 1994), and/or the ADOS-G (Autism Diagnosis Observation Schedule, Lord et al. 1989), or the AAA (Adult Asperger Assessment, Baron-Cohen et al. 2005). Participants gave their written

informed consent beforehand. Approval was obtained from the local ethics committee (South East IV Committee for the Protection of Persons).

### ***Glasgow Sensory Questionnaire***

Participants completed the Glasgow Sensory Questionnaire (Robertson and Simmons 2013), a 42-question questionnaire assessing hypersensitivity and hyposensitivity in seven sensory modalities, including the tactile sensory modality. We calculated the GSQ scores of hypersensitivity and hyposensitivity in total (maximum score: 84), and in the tactile modality (maximum score: 12). One of the ASD participants has not completed the GSQ questionnaire.

### ***Tactile stimuli***

Tactile stimulations were delivered on the left second finger, using a piezo-electric tactile stimulator (mPTS, Dancer Design <http://www.dancerdesign.co.uk>) associated with Presentation (<https://www.neurobs.com/>). Tactile stimuli are described in the fMRI section.

### ***Tactile threshold measurements***

Thresholds were measured at 30Hz and 200Hz on the second finger outside of the MRI scanner, following the classical staircase procedure described in the fMRI section. Stimulation intensity increased/decreased by steps of 0.050 in the 30Hz condition, and by steps of 0.025 in the 200Hz condition (Blakemore et al. 2006).

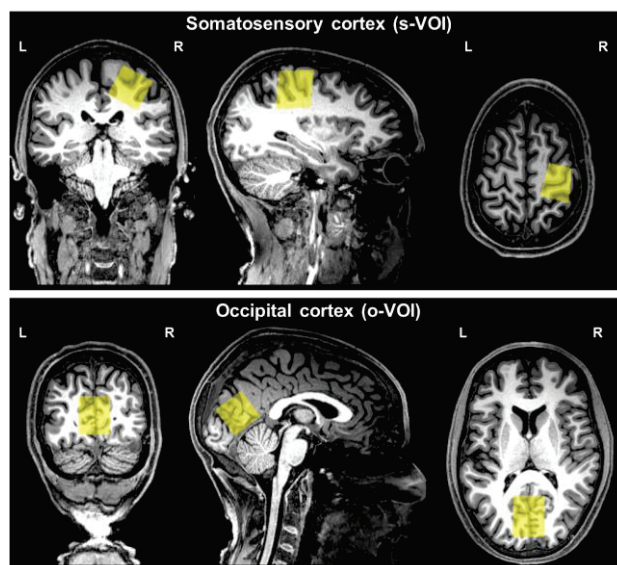
### ***Tactile discrimination task***

Participants performed a task designed to elicit a time-order effect. The task has been described in the fMRI task of the same chapter. Computational models were used to estimate the precision of sensory encoding, modeled by  $\pi_s$ , and the influence of priors on perceptual decision, modeled by  $\gamma$ . Here, we consider these parameters in the stable session only (run 1, 2, and beginning of 3) to avoid any influence of prior adjustment in changing contexts. Higher  $\pi_s$  correspond to high sensory precision, and high  $\gamma$  correspond to high influence of priors on perceptual decisions.

### ***MRI and MRS acquisitions***

MRI and MRS data were acquired on a 3 Tesla Siemens Magnetom Prisma scanner, with a 64-channel head-neck coil. A 3D whole brain T1-weighted anatomical image was obtained for each subject, using a MPRAGE sequence (Repetition time TR = 3500ms; Echo time TE = 3.42ms; FOV = 224mm; 192 slices; voxel size = 0.9 x 0.9 x 0.9 mm).

Single voxel MR spectra were acquired from two 3x3x3cm volumes of interest located in the right somatosensory cortex (s-VOI) and in the median occipital cortex, as a control region (o-VOI) (Figure 2). The s-VOI was centered on the hand knob of the right postcentral gyrus and parallel to the cortical surface. Because of the VOI size and postcentral gyrus shape, the s-VOI overlapped some regions belonging to the precentral gyrus. The o-VOI was set in the occipital lobe, in the median region,



*Figure 2: VOI placement in the MRS study*

dorsal to the cerebellum. Its posterior limit was the superior sagittal sinus. During the MRS acquisition of the s-VOI, participants performed a tactile threshold measurement task. During the acquisition of the o-VOI, participants watched a documentary.

Prior to this main acquisition, we performed shims adjustment and a quality-check MRS acquisition. Shims were adjusted using the automatic GRE shim sequence, and we ensured that shimming for the full width at maximum of water signal was inferior to 16Hz. In order to make sure that there were no lipid contaminations or contamination from the venous sinus in the o-VOI, we ran a short quality-check MRS acquisition (4 excitations) beforehand. MR spectra were collected using the MEGA-PRESS (Mescher et al. 1998) spectral editing sequence with TE = 68ms, TR = 2000ms, 160 pairs of interleaved spectra, 2048 datapoints, 5 kHz spectral width and center frequency set to the peak position of creatine at -1.7ppm relative to the water. The GABA spectrum was obtained by subtracting the edit-ON and edit-OFF spectra (ordered OFF-first in the acquisition), after having applied a 21.5ms (55Hz) frequency-selective editing pulse at 1.9 and 7.5ppm in alternating spectral lines.

An additional localized unsuppressed water scan was acquired in order to have a fully relaxed water measurement, with TE = 30ms, TR = 10 000ms and four averages. The overall acquisition time per voxel was inferior to 15 minutes. The acquisition parameters were chosen after the study by Robertson and colleagues (Robertson et al. 2016).

### ***MRS analysis and quantification***

MRS original data (*.dat*) were preprocessed using the FID-A toolkit (Simpson et al. 2017). FID-A preprocessing was made in seven steps: (1) multi-coil combination, (2)

removing motion corrupted averages, with a criteria of more than 3 standard deviations from the mean, (3) realignment of averages after frequency and phase drift correction, (4) removing points before and after TE (0 points), (5) zero-order phase correction using the creatine peak, (6) alignment of the edit-ON and edit-OFF spectra, (7) subtraction of edit-ON and edit-OFF spectra. Each fit was carefully individually inspected. The fits of 2 NT and 2 ASD subjects were not satisfying, suggesting lipid contaminations due to movements during the MRS acquisition. These four participants were discarded from the analyses. On average, eleven pairs of scans were removed in each group after step 2 ( $22 \pm 14$  scans in the NT group,  $22 \pm 12$  scans in the ASD group). The preprocessed data were saved as Matlab structures to be processed in Gannet (Edden et al. 2014).

FID-A preprocessed data were implemented in Gannet GABA analysis toolkit (Edden et al. 2014) to estimate GABA levels, with the unsuppressed water scan as water reference. GABA concentrations were corrected for tissue fractions using the segmentation and quantification steps implemented in Gannet (Harris et al. 2015). These steps included tissue segmentation in SPM (SPM8, Wellcome Trust Center for Neuroimaging) to estimate the fractions in grey matter  $f_{GM}$ , white matter  $f_{WM}$  and cerebrospinal fluid  $f_{CSF}$ . We used the latest tissue correction (Harris et al. 2015) with  $\alpha = 0.5$ , which is written as follows:  $[GABA]_{\alpha corr} = \frac{[GABA]}{f_{GM} + \alpha \cdot f_{WM}}$ . GABA concentrations are given in institutional units (*i.u.*).

Glutamate concentrations were estimated from the edit-OFF spectra using Tarquin (Wilson et al. 2011), with the unsuppressed water scan as water reference. Preprocessing options included Eddy current correction and lipid filter.

To fit the data, water concentration was set individually depending on the tissue fractions of the volume of interest. For each subject, water concentration was calculated as follows:  $mean[c_{water}(d_{waterGM} \cdot f_{GM} + d_{waterWM} \cdot f_{WM} + d_{waterCSF} \cdot f_{CSF})]$ , with a water concentration  $c_{water}$  of 55550mM and water densities of 0.78 in the grey matter ( $d_{waterGM}$ ), 0.65 in the white matter ( $d_{waterWM}$ ), and 0.97 in the cerebrospinal fluid ( $d_{waterCSF}$ ) (Gasparovic et al. 2009). Glutamate concentrations are given in arbitrary units (*a.u.*). Note that GABA and glutamate levels cannot be compared as they do not rely on the same analysis method.

### **Statistical analyses**

Concentrations in neurotransmitters were compared between groups using Student t-test. Correlations between concentrations and behavioral measures were performed using Pearson correlation test. An ANOVA analysis of the factors group (NT and ASD) and frequency (30Hz and 200Hz) was done to assess changes in perceptual thresholds. Bayesian

model averaging for frequencies ranging from 24 to 32Hz was done to estimate  $\gamma$  and  $\pi_s$ , following the same procedure as in the fMRI study. All statistical analyses were performed using R (<http://www.r-project.org/>, version 3.3.1.) and the threshold for statistical significance was set at  $p < .05$ .

## Results

### **MR spectroscopy measures**

#### ***Tissue fractions***

In the s-VOI, tissue fractions in grey matter, white matter and cerebrospinal fluid were respectively 33% ( $\pm 3$ ), 58% ( $\pm 5$ ) and 9% ( $\pm 3$ ) in the NT group, and 31% ( $\pm 4$ ), 61% ( $\pm 5$ ) and 8% ( $\pm 3$ ) in the ASD group. In the o-VOI, tissue fractions in grey matter, white matter and cerebrospinal fluid were respectively 60% ( $\pm 3$ ), 32% ( $\pm 3$ ) and 7% ( $\pm 1$ ) in the NT group, and 60% ( $\pm 2$ ), 32% ( $\pm 3$ ) and 7% ( $\pm 2$ ) in the ASD group. These fractions did not differ between groups. GABA and glutamate concentrations were corrected for tissue fractions, as described in the Method section.

#### ***GABA fit***

We visually ensured that every fit was close to the expected fit aspect. GABA fit errors estimated in Gannet in the NT and ASD groups were respectively 5.6 ( $\pm 1.5$ ) and 6.4 ( $\pm 2.7$ ) in the s-VOI, and 4.7 ( $\pm 1.2$ ) and 4.8 ( $\pm 1.2$ ) in the o-VOI.

Water error fits for NT and ASD groups were respectively, 0.4 ( $\pm 0.1$ ) and 0.4 ( $\pm 0.2$ ) in the s-VOI, and 0.5 ( $\pm 0.1$ ) and 0.4 ( $\pm 0.1$ ) in the o-VOI.

In the s-VOI, GABA concentrations were 2.85 ( $\pm 0.86$ ) *i.u.* in the NT group, and 2.37 ( $\pm 0.52$ ) *i.u.* in the ASD group (Figure 2). The ASD group had a lower GABA concentration than the NT group ( $p < .05$ ). In the o-VOI, GABA concentrations were 2.22 ( $\pm 0.51$ ) *i.u.* in the NT group, and 2.35 ( $\pm 0.67$ ) *i.u.* in the ASD group, and did not differ between groups.

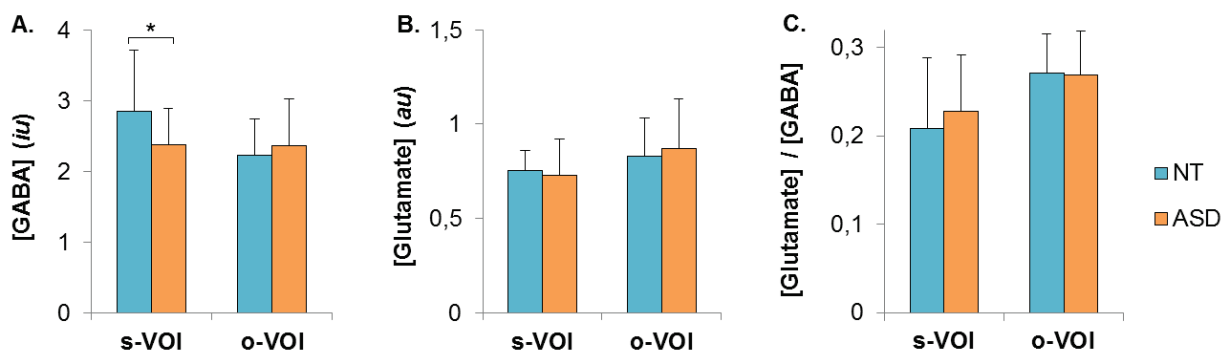
#### ***Glutamate fit***

We visually ensured that every fit was close to the expected fit aspect. In the s-VOI, glutamate concentrations were 0.55 ( $\pm 0.14$ ) *a.u.* in the NT group, and 0.53 ( $\pm 0.15$ ) *a.u.* in the ASD group (Figure 2). In the o-VOI, glutamate concentrations were 0.83 ( $\pm 0.20$ ) *a.u.* in the NT group, and 0.87 ( $\pm 0.26$ ) *a.u.* in the ASD group. Glutamate concentrations did not differ

between groups. Noticeably, one of the NT subjects had an s-VOI glutamate concentration which appeared to be particularly low (0.1 *a.u.*) despite a correct aspect of the glutamate fit.

### **Glutamate/GABA ratio**

The glutamate/GABA ratio did not differ between groups in the s-VOI (NT: 0.21  $\pm$ 0.08, ASD: 0.23  $\pm$ 0.06) nor in the o-VOI (NT: 0.27  $\pm$ 0.04, ASD: 0.27  $\pm$ 0.05) (Figure 3). GABA concentrations in o-VOI and s-VOI did not correlate within group, nor did the glutamate concentrations. In the s-VOI, glutamate and GABA concentrations did not correlate. However, glutamate and GABA concentrations were strongly correlated in the o-VOI (2 groups:  $r = .83, p < 10^{-6}$ , NT:  $r = .80, p < 10^{-5}$ , ASD:  $r = .86, p < 10^{-5}$ ).



**Figure 3: MRS measurements in the somatosensory VOI (s-VOI) and occipital VOI (o-VOI)** GABA concentration (A), glutamate concentration (B), and glutamate/GABA ratio (C) in the NT and ASD groups.

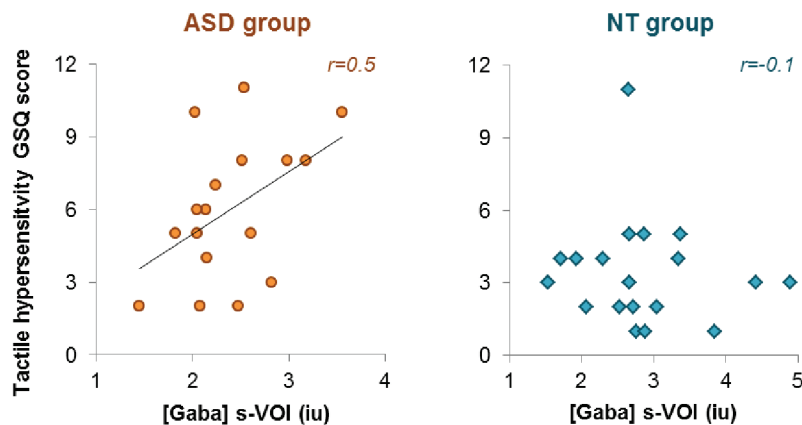
## **Correlations between MRS and sensory sensitivity**

### **Self-reported hypersensitivity**

Hypersensitivity total GSQ score and tactile GSQ score were 20.8 ( $\pm$ 9.4) and 3.4 ( $\pm$ 2.3) in NT, and 39.3 ( $\pm$ 13.7) and 6.0 ( $\pm$ 2.9) in ASD. Hyposensitivity total GSQ score and tactile GSQ score were 18.8 ( $\pm$ 7.3) and 3.6 ( $\pm$ 2.1) in NT, and 31.8 ( $\pm$ 9.0) and 4.8 ( $\pm$ 2.0) in ASD. The two total scores were higher in ASD than NT ( $p < .001$ ), the tactile hypersensitivity score was higher in ASD than NT ( $p < .01$ ) but no difference were found between tactile hyposensitivity scores between groups.

Hence, we investigated correlations between hypersensitivity scores and GABA to assess whether a different GABAergic modulation could explain group differences. No significant correlations were found between GSQ scores and GABA concentration in the NT group. Yet, in the ASD group, the s-VOI GABA concentration positively correlated with the

hypersensitivity total GSQ score ( $r = .54, p < .05$ ) and tactile GSQ score ( $r = .47, p = 0.059$ ) (Figure 4). These measures did not correlate with GABA concentrations in o-VOI.



**Figure 4: Correlations between GABA concentrations in the somatosensory cortex and GSQ scores of tactile hypersensitivity.** High GSQ scores indicate high hypersensitivity

### Perceptual thresholds

#### Average threshold

At 30Hz and 200Hz, the average perception thresholds were respectively 0.45 ( $\pm 0.19$ ) and 0.27 ( $\pm 0.11$ ) in the NT group, and to 0.34 ( $\pm 0.13$ ) and 0.22 ( $\pm 0.10$ ) in the ASD group. An ANOVA analysis of the factors group and frequency (30Hz vs. 200Hz) on threshold revealed a group effect ( $F(1,42) = 23.6, p < 10^{-4}$ ), a frequency effect ( $F(1,42) = 75.8, p < 10^{-6}$ ), and a trend toward an interaction between frequency and group ( $F(1,42) = 3.2, p = 0.08$ ). Pairwise t-test revealed that both NT and ASD subjects had a lower threshold at 200Hz than at 30Hz (NT:  $p < 10^{-5}$ , ASD:  $p < 10^{-4}$ ). The ASD group had lower thresholds than NT, with significant differences for the 30Hz threshold ( $p < .05$ ).

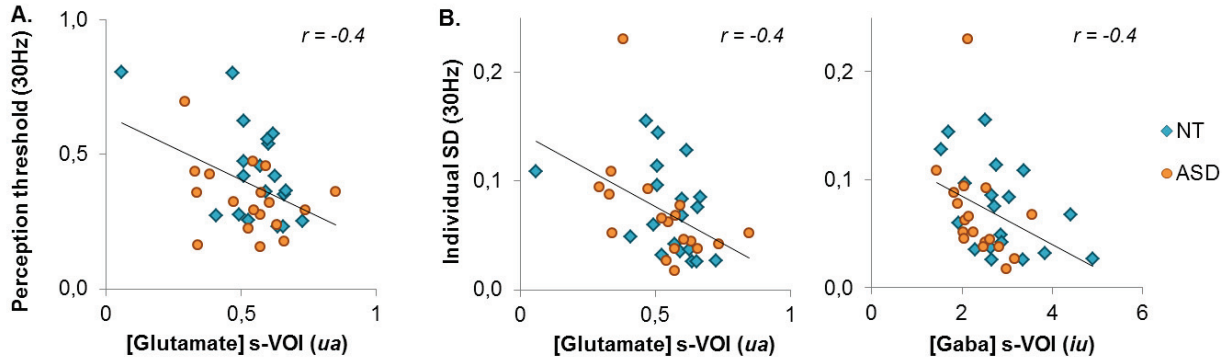
Perception thresholds at 30Hz did not correlate with s-VOI GABA concentrations, but negatively correlated with glutamate concentrations (2 groups:  $r = -.42, p < .01$ , NT:  $r = -.42, p < .01$ ) (Figure 5). However, in NT, the thresholds also correlated with glutamate concentration in the o-VOI ( $r = -.76, p < .001$ ). No significant correlations were found between thresholds and glutamate/GABA ratio in any group.

#### Variability on threshold measurement

At 30Hz and 200Hz, the individual standard deviation (SD) on threshold measurements were respectively 0.07 ( $\pm 0.04$ ) and 0.04 ( $\pm 0.02$ ) in NT, and 0.07 ( $\pm 0.04$ ) and 0.05 ( $\pm 0.03$ ) in ASD. An ANOVA analysis of the factors group and frequency on individual SD only revealed a frequency effect ( $F(1,42) = 22.0, p < 10^{-4}$ ). Pairwise t-test revealed a lower individual SD at 200Hz than 30Hz ( $p < .01$  in the NT group,  $p < .05$  in the ASD group).



SD at 30Hz was negatively correlated with GABA concentrations (2 groups:  $r = -.38$ ,  $p < .05$ , NT:  $r = -.47$ ,  $p < .05$ , ASD:  $r = -.40$ ,  $p = .10$ ) and glutamate concentrations (2 groups:  $r = -.45$ ,  $p < .01$ , NT:  $r = -.38$ ,  $p = .11$ , ASD:  $r = -.52$ ,  $p < .05$ ) (Figure 5). Yet, in the NT group, these correlations were also significant with concentrations measured in o-VOI (GABA:  $r = -.62$ ,  $p < .01$ , glutamate:  $r = -.69$ ,  $p < .001$ ).

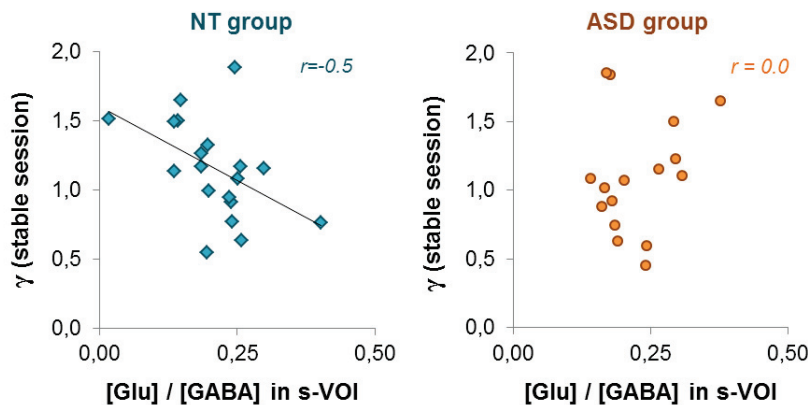


**Figure 5: Correlations between MRS measurements and threshold measurements**

- A. Correlation between the mean perception threshold at 30Hz and glutamate concentration in the somatosensory VOI (s-VOI)
- B. Correlations between the individual standard deviation (SD) during threshold measurements at 30Hz and glutamate (left) or GABA (right) concentrations in the s-VOI.

### Correlation between MRS measurements and model parameters

In the stable session, the time-order parameter  $\gamma$  (reflecting prior influence) did not differ between groups (NT:  $\gamma = 1.2 \pm 0.4$ , ASD:  $\gamma = 1.2 \pm 0.5$ ). Increases in prior influence could be mediated by increased suppressive field gain (Rosenberg et al. 2015), seen by a decreased glutamate/GABA ratio. Hence, we investigated whether an increase in  $\gamma$  could be linked to a decreased glutamate/GABA ratio. There was indeed a negative correlation between  $\gamma$  and s-VOI glutamate/GABA ratio in the NT group ( $r = -.48$ ,  $p < .05$ ), but not in the ASD group.  $\gamma$  did not correlate with this ratio in the o-VOI in any group. Finally, the precision parameter  $\pi_s$  ( $8.0 \pm 3.8$  in NT,  $6.8 \pm 4.8$  in ASD) did not correlate with glutamate/GABA ratio.



**Figure 5: Correlations between the glutamate / GABA ratio and  $\gamma$ .** High  $\gamma$  indicates an increased influence of priors on perceptual decision.

## *Discussion*

This MRS study aimed at measuring GABA and glutamate levels in ASD and determining whether these correlations were associated with changes in tactile sensitivity and perceptual inference between individuals. In the somatosensory cortex, adults with ASD had lower GABA levels than controls, and similar glutamate levels. Higher GABA concentrations were associated with higher tactile hypersensitivity in the ASD group only, and with increased precision in measurements of tactile perception thresholds at 30Hz (significant in NT, tendency in ASD). Higher glutamate concentrations were associated with lower perception thresholds at 30Hz in NT, and with higher precision in the measurement of perception thresholds (significant in ASD, tendency in NT). Finally, we found a negative correlation between a measure of prior weight on perceptual decision and glutamate/GABA ratio in NT subjects only.

First, adults with ASD had reduced GABA levels in the somatosensory cortex, as found in children with ASD (Puts et al. 2016). Puts and colleagues found a decrease by 8% between control and ASD children, and we found a decrease by 17% between control and ASD adults. Note that our measurements slightly from theirs on the delimitation of the VOI and on the preprocessing steps. We also confirmed that adults with ASD do not have a decreased concentration of glutamate or GABA in the occipital cortex (Robertson et al. 2016). Decreased GABA levels in adults with ASD may affect the excitatory/inhibitory modulation of messages passing through the somatosensory cortex. Given differences in GABA concentrations, we wondered how it could affect sensory sensitivity and prior influence on perception in ASD and NT subjects.

Decreased variability in the measurement of the perception threshold at 30Hz was associated with increased glutamate and GABA levels in both groups (correlations with GABA in ASD and with glutamate in NT were non-significant tendencies). We can interpret that high glutamate and GABA concentrations lead to an increased signal-to-noise ratio. In this view, we can interpret the positive correlation between hypersensitivity (measured with the GSQ) and GABA levels in ASD as an increased precision of the sensory stimuli leading to hypersensitivity and hyper-responsiveness in ASD. In control adults, we did not evidence any link between hypersensitivity and GABA concentrations, suggesting that GABA action on hypersensitivity differed between groups, at least in the tactile modality.

Furthermore, high glutamate concentrations were associated with low thresholds of perception, suggesting that a higher level of excitatory signals promotes the detection of

stimuli at lower thresholds. However, we must be cautious about the interpretation of this correlation as it seems to be mostly driven by one ASD and two NT subjects. Additionally, in NT, lower tactile thresholds were also associated with increased glutamate in the occipital cortex, showing that this relationship was not specific to glutamate levels in the somatosensory cortex.

Perception thresholds at 200Hz were lower than those at 30Hz in both groups, replicating the finding that NT and ASD subjects have lower thresholds at 200Hz (Blakemore et al. 2006). However, we did not find any difference in thresholds at 200Hz between groups, contrary to Blakemore and colleagues who suggested that Pacinian corpuscles (activated at 200Hz) might have lower activation threshold in ASD. We could have expected that the correlations found between neurotransmitter levels and perception thresholds to be similar at 30Hz and 200Hz, but only correlations with thresholds at 30Hz were found. It might be explained by a reduced dispersal of the thresholds (standard deviation of NT: 0.2 for the 30Hz thresholds, 0.1 for the 200Hz thresholds) preventing from making correlations, or by another modulatory processes.

Besides, we aimed at understanding whether the glutamate/GABA ratio modulated the parameters estimated in our model of perceptual decision. The main parameter that we wanted to test was  $\gamma$ , a parameter assessing the amplitude of the time-order effect and so, assessing the influence of priors on perceptual decisions. According to the simulations by Rosenberg and colleagues, we had assumed that increased  $\gamma$  (high prior weight) would be associated with decreased glutamate/GABA (Rosenberg et al. 2015). We confirmed this hypothesis as higher  $\gamma$  were associated with decreased glutamate/GABA ratio in NT participants only. This result suggests that increases in suppressive field gain could explain different weight of priors on perceptual decision between control individuals. It also suggests that glutamate/GABA action on perceptual decision involving prior knowledge could be abnormal in ASD. Differences in prior weights between individuals with ASD could be mediated by other neurotransmitters, such as noradrenaline, acetylcholine or dopamine (Iglesias et al. 2013; Lawson et al. 2014; Moran et al. 2013; Van de Cruys et al. 2014). According to computational simulations by Yu and Dayan (2005), acetylcholine would encode expected uncertainty whereas norepinephrine would track unexpected uncertainty. Additionally, high acetylcholine concentration would be associated with stronger prediction errors (Moran et al. 2013). Contrary to GABA and glutamate, acetylcholine and noradrenaline concentrations cannot be measured *in vivo* by non-invasive methods, but can only be approached by pharmaceutical modulations.

Exploring the same correlations in other sensory modalities would be useful to figure out if these processes are generalizable.

An important limitation to MRS studies is that it only gives a single measure of concentration per participant, and cannot capture their modulations during perceptual processes. Hence, it simply gives a global overview of how concentration in neuromodulators could explain differences between individuals. In perceptual decisions, there would be a fine regulation of the relative weights of sensory inputs and priors, which would change over time, depending on the type of sensory input and on the previously learnt priors. This precise regulation is made dynamically, which cannot be assessed by MRS. Two individuals could have similar GABA concentrations measured by MRS, while one would have a high modulation during the task, whereas the other would not have any. To disentangle hypothesis of perceptual inference in ASD, we need to have access to dynamic measurements of these neuromodulations. Some emerging studies intend to develop dynamic glutamate MRS measurements through functional magnetic resonance spectroscopy, but it remains quite preliminary (Apšvalka et al. 2015). In addition, even if we had dynamic measurements of glutamate or GABA, the MRS measurements might not be sensitive enough to be able to capture the small changes in glutamate/GABA concentrations depending on the relative weighting of priors and sensory inputs. Furthermore, MRS measures give an indication of the GABA and glutamate levels in a large volume of interest but cannot reveal if these neurotransmitters are simply stocked in neurons or glial cells or if they are released in synapses, modulating neurotransmission.

Despite these limitations, MRS offers a first attempt to understand how differences in neurotransmitter concentrations between individuals could explain observed behaviors. It is also an opportunity to accumulate additional evidence to propose a complete model of ASD, taking into account every scale.

## References

- American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders*. American Psychiatric Association. <http://dsm.psychiatryonline.org/doi/book/10.1176/appi.books.9780890425596>. Accessed 24 September 2015
- Apšvalka, D., Gadie, A., Clemence, M., & Mullins, P. G. (2015). Event-related dynamics of glutamate and BOLD effects measured using functional magnetic resonance spectroscopy (fMRS) at 3T in a repetition suppression paradigm. *NeuroImage*, 118, 292–300. doi:10.1016/j.neuroimage.2015.06.015
- Baron-Cohen, S., Wheelwright, S., Robinson, J., & Woodbury-Smith, M. (2005). The Adult Asperger Assessment (AAA): a diagnostic method. *Journal of Autism and Developmental Disorders*, 35(6), 807–819. doi:10.1007/s10803-005-0026-5
- Ben-Ari, Y., Khalilov, I., Kahle, K. T., & Cherubini, E. (2012). The GABA excitatory/inhibitory shift in brain maturation and neurological disorders. *The Neuroscientist: A Review Journal Bringing Neurobiology, Neurology and Psychiatry*, 18(5), 467–486. doi:10.1177/1073858412438697
- Bittigau, P., & Ikonomidou, C. (1997). Glutamate in neurologic diseases. *Journal of Child Neurology*, 12(8), 471–485.
- Blakemore, S.-J., Tavassoli, T., Calò, S., Thomas, R. M., Catmur, C., Frith, U., & Haggard, P. (2006). Tactile sensitivity in Asperger syndrome. *Brain and cognition*, 61(1), 5–13. doi:10.1016/j.bandc.2005.12.013
- Brock, J. (2012). Alternative Bayesian accounts of autistic perception: comment on Pellicano and Burr. *Trends in Cognitive Sciences*, 16(12), 573–574. doi:10.1016/j.tics.2012.10.005
- Davis, G., & Plaisted-Grant, K. (2015). Low endogenous neural noise in autism. *Autism: The International Journal of Research and Practice*, 19(3), 351–362. doi:10.1177/1362361314552198
- Du, L., Shan, L., Wang, B., Li, H., Xu, Z., Staal, W. G., & Jia, F. (2015). A Pilot Study on the Combination of Applied Behavior Analysis and Bumetanide Treatment for Children with Autism. *Journal of Child and Adolescent Psychopharmacology*, 25(7), 585–588. doi:10.1089/cap.2015.0045
- Edden, R. A. E., Muthukumaraswamy, S. D., Freeman, T. C. A., & Singh, K. D. (2009). Orientation discrimination performance is predicted by GABA concentration and gamma oscillation frequency in human primary visual cortex. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, 29(50), 15721–15726. doi:10.1523/JNEUROSCI.4426-09.2009
- Edden, R. A. E., Puts, N. A. J., Harris, A. D., Barker, P. B., & Evans, C. J. (2014). Gannet: A batch-processing tool for the quantitative analysis of gamma-aminobutyric acid-edited MR spectroscopy spectra. *Journal of magnetic resonance imaging: JMRI*, 40(6), 1445–1452.
- El-Ansary, A., & Al-Ayadhi, L. (2014). GABAergic/glutamatergic imbalance relative to excessive neuroinflammation in autism spectrum disorders. *Journal of Neuroinflammation*, 11, 189. doi:10.1186/s12974-014-0189-0
- Fatemi, S. H., Halt, A. R., Stary, J. M., Kanodia, R., Schulz, S. C., & Realmuto, G. R. (2002). Glutamic acid decarboxylase 65 and 67 kDa proteins are reduced in autistic parietal and cerebellar cortices. *Biological Psychiatry*, 52(8), 805–810.
- Fatemi, S. H., Reutiman, T. J., Folsom, T. D., Rustan, O. G., Rooney, R. J., & Thuras, P. D. (2014). Downregulation of GABAA Receptor Protein Subunits  $\alpha 6$ ,  $\beta 2$ ,  $\delta$ ,  $\epsilon$ ,  $\gamma 2$ ,  $\theta$ , and  $\rho 2$  in Superior Frontal Cortex of Subjects with Autism. *Journal of Autism and Developmental Disorders*, 44(8), 1833–1845. doi:10.1007/s10803-014-2078-x
- Gaetz, W., Bloy, L., Wang, D. J., Port, R. G., Blaskey, L., Levy, S. E., & Roberts, T. P. L. (2014). GABA estimation in the brains of children on the autism spectrum: measurement precision and regional cortical variation. *NeuroImage*, 86, 1–9. doi:10.1016/j.neuroimage.2013.05.068
- García-Pérez, M. A. (1998). Forced-choice staircases with fixed step sizes: asymptotic and small-sample properties. *Vision Research*, 38(12), 1861–1881.
- Gasparovic, C., Neeb, H., Feis, D. L., Damaraju, E., Chen, H., Doty, M. J., et al. (2009). Quantitative spectroscopic imaging with in situ measurements of tissue water T1, T2, and density. *Magnetic Resonance in Medicine*, 62(3), 583–590. doi:10.1002/mrm.22060

- Han, S., Tai, C., Jones, C. J., Scheuer, T., & Catterall, W. A. (2014). Enhancement of inhibitory neurotransmission by GABAA receptors having  $\alpha 2,3$ -subunits ameliorates behavioral deficits in a mouse model of autism. *Neuron*, 81(6), 1282–1289. doi:10.1016/j.neuron.2014.01.016
- Harada, M., Taki, M. M., Nose, A., Kubo, H., Mori, K., Nishitani, H., & Matsuda, T. (2011). Non-invasive evaluation of the GABAergic/glutamatergic system in autistic patients observed by MEGA-editing proton MR spectroscopy using a clinical 3 tesla instrument. *Journal of Autism and Developmental Disorders*, 41(4), 447–454. doi:10.1007/s10803-010-1065-0
- Harris, A. D., Puts, N. A. J., & Edden, R. A. E. (2015). Tissue correction for GABA-edited MRS: Considerations of voxel composition, tissue segmentation, and tissue relaxations. *Journal of magnetic resonance imaging: JMRI*, 42(5), 1431–1440. doi:10.1002/jmri.24903
- Hohwy, J., Roepstorff, A., & Friston, K. (2008). Predictive coding explains binocular rivalry: an epistemological review. *Cognition*, 108(3), 687–701. doi:10.1016/j.cognition.2008.05.010
- Hussman, J. P. (2001). Suppressed GABAergic inhibition as a common factor in suspected etiologies of autism. *Journal of Autism and Developmental Disorders*, 31(2), 247–248.
- Iglesias, S., Mathys, C., Brodersen, K. H., Kasper, L., Piccirelli, M., den Ouden, H. E. M., & Stephan, K. E. (2013). Hierarchical prediction errors in midbrain and basal forebrain during sensory learning. *Neuron*, 80(2), 519–530. doi:10.1016/j.neuron.2013.09.009
- Lam, K. S. L., Aman, M. G., & Arnold, L. E. (2006). Neurochemical correlates of autistic disorder: a review of the literature. *Research in developmental disabilities*, 27(3), 254–289. doi:10.1016/j.ridd.2005.03.003
- Lawson, R. P., Rees, G., & Friston, K. J. (2014). An aberrant precision account of autism. *Frontiers in Human Neuroscience*, 8, 302. doi:10.3389/fnhum.2014.00302
- Lemonnier, E., & Ben-Ari, Y. (2010). The diuretic bumetanide decreases autistic behaviour in five infants treated during 3 months with no side effects. *Acta Paediatrica (Oslo, Norway: 1992)*, 99(12), 1885–1888. doi:10.1111/j.1651-2227.2010.01933.x
- Lord, C., Rutter, M., Goode, S., Heemsbergen, J., Jordan, H., Mawhood, L., & Schopler, E. (1989). Autism diagnostic observation schedule: a standardized observation of communicative and social behavior. *Journal of Autism and Developmental Disorders*, 19(2), 185–212.
- Lord, C., Rutter, M., & Le Couteur, A. (1994). Autism Diagnostic Interview-Revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *Journal of Autism and Developmental Disorders*, 24(5), 659–685.
- Ma, D. Q., Whitehead, P. L., Menold, M. M., Martin, E. R., Ashley-Koch, A. E., Mei, H., et al. (2005). Identification of Significant Association and Gene-Gene Interaction of GABA Receptor Subunit Genes in Autism. *The American Journal of Human Genetics*, 77(3), 377–388. doi:10.1086/433195
- Mescher, M., Merkle, H., Kirsch, J., Garwood, M., & Gruetter, R. (1998). Simultaneous in vivo spectral editing and water suppression. *NMR in biomedicine*, 11(6), 266–272.
- Moran, R. J., Campo, P., Symmonds, M., Stephan, K. E., Dolan, R. J., & Friston, K. J. (2013). Free energy, precision and learning: the role of cholinergic neuromodulation. *The Journal of neuroscience: the official journal of the Society for Neuroscience*, 33(19), 8227–8236. doi:10.1523/JNEUROSCI.4255-12.2013
- Pellicano, E., & Burr, D. (2012). When the world becomes “too real”: a Bayesian explanation of autistic perception. *Trends in cognitive sciences*, 16(10), 504–510. doi:10.1016/j.tics.2012.08.009
- Piton, A., Jouan, L., Rochefort, D., Dobrzyniecka, S., Lachapelle, K., Dion, P. A., et al. (2013). Analysis of the effects of rare variants on splicing identifies alterations in GABAA receptor genes in autism spectrum disorder individuals. *European Journal of Human Genetics*, 21(7), 749–756. doi:10.1038/ejhg.2012.243
- Puts, N. A. J., & Edden, R. A. E. (2012). In vivo magnetic resonance spectroscopy of GABA: a methodological review. *Progress in Nuclear Magnetic Resonance Spectroscopy*, 60, 29–41. doi:10.1016/j.pnmrs.2011.06.001
- Puts, N. A. J., Edden, R. A. E., Evans, C. J., McGlone, F., & McGonigle, D. J. (2011). Regionally Specific Human GABA Concentration Correlates with Tactile Discrimination Thresholds. *The Journal of Neuroscience*, 31(46), 16556–16560. doi:10.1523/JNEUROSCI.4489-11.2011
- Puts, N. A. J., Wodka, E. L., Harris, A. D., Crocetti, D., Tommerdahl, M., Mostofsky, S. H., & Edden, R. A. E. (2016). Reduced GABA and altered somatosensory function in children with autism spectrum disorder. *Autism Research: Official Journal of the International Society for Autism Research*. doi:10.1002/aur.1691

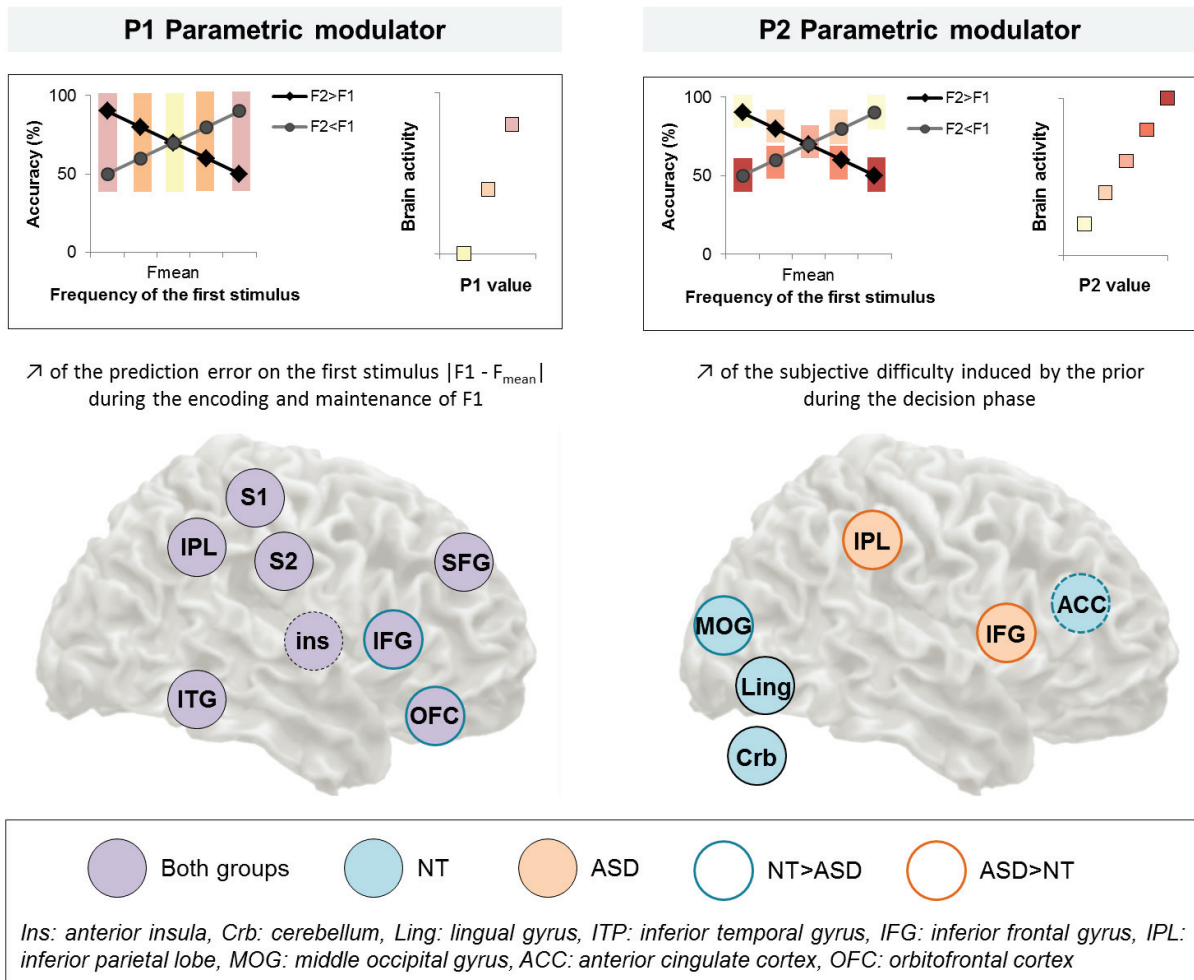
- Robertson, A. E., & Simmons, D. R. (2013). The Relationship between Sensory Sensitivity and Autistic Traits in the General Population. *Journal of Autism and Developmental Disorders*, 43(4), 775–784. doi:10.1007/s10803-012-1608-7
- Robertson, C. E., Ratai, E.-M., & Kanwisher, N. (2016). Reduced GABAergic Action in the Autistic Brain. *Current Biology*, 26(1), 80–85. doi:10.1016/j.cub.2015.11.019
- Rosenberg, A., Patterson, J. S., & Angelaki, D. E. (2015). A computational perspective on autism. *Proceedings of the National Academy of Sciences of the United States of America*, 112(30), 9158–9165. doi:10.1073/pnas.1510583112
- Rubenstein, J. L. R., & Merzenich, M. M. (2003). Model of autism: increased ratio of excitation/inhibition in key neural systems. *Genes, Brain, and Behavior*, 2(5), 255–267.
- Shao, Y., Cuccaro, M. L., Hauser, E. R., Raiford, K. L., Menold, M. M., Wolpert, C. M., et al. (2003). Fine Mapping of Autistic Disorder to Chromosome 15q11-q13 by Use of Phenotypic Subtypes. *The American Journal of Human Genetics*, 72(3), 539–548. doi:10.1086/367846
- Simmons, D. R., McKay, L., McAleer, P., Toal, E., Robertson, A., & Pollick, F. E. (2007). Neural noise and autism spectrum disorders. *Perception*, 36, 119–120.
- Simmons, D. R., Robertson, A. E., McKay, L. S., Toal, E., McAleer, P., & Pollick, F. E. (2009). Vision in autism spectrum disorders. *Vision research*, 49(22), 2705–2739. doi:10.1016/j.visres.2009.08.005
- Simpson, R., Devenyi, G. A., Jezzard, P., Hennessy, T. J., & Near, J. (2017). Advanced processing and simulation of MRS data using the FID appliance (FID-A)-An open source, MATLAB-based toolkit. *Magnetic Resonance in Medicine*, 77(1), 23–33. doi:10.1002/mrm.26091
- Van de Cruys, S., Evers, K., Van der Hallen, R., Van Eylen, L., Boets, B., de-Wit, L., & Wagemans, J. (2014). Precise minds in uncertain worlds: predictive coding in autism. *Psychological Review*, 121(4), 649–675. doi:10.1037/a0037665
- Wilson, M., Reynolds, G., Kauppinen, R. A., Arvanitis, T. N., & Peet, A. C. (2011). A constrained least-squares approach to the automated quantitation of in vivo 1H magnetic resonance spectroscopy data. *Magnetic Resonance in Medicine*, 65(1), 1–12. doi:10.1002/mrm.22579
- Yizhar, O., Fenno, L. E., Prigge, M., Schneider, F., Davidson, T. J., O’Shea, D. J., et al. (2011). Neocortical excitation/inhibition balance in information processing and social dysfunction. *Nature*, 477(7363), 171–178. doi:10.1038/nature10360
- Yu, A. J., & Dayan, P. (2005). Uncertainty, neuromodulation, and attention. *Neuron*, 46(4), 681–692. doi:10.1016/j.neuron.2005.04.026

## Synthesis

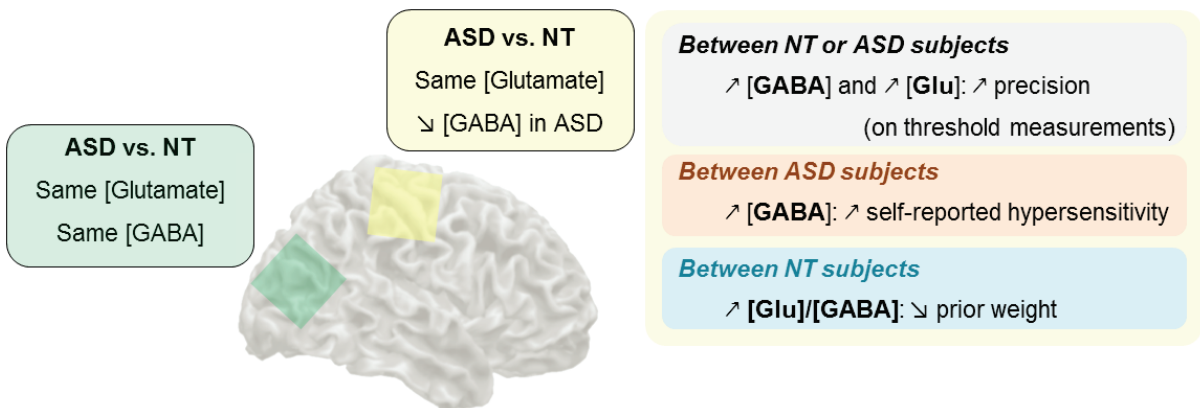
### ◆ Behavioral level:

▷ Reduced flexibility in subjects with ASD to adapt their priors in changing contexts

### ◆ Neural level:



### ◆ Molecular level







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## GENERAL DISCUSSION

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## 1. Summary

This thesis aimed at characterizing perceptual inference and learning in adults with autism spectrum disorder, within the Bayesian brain framework. In this framework, perception results from an interplay between weighted contributions of sensory inputs and prior knowledge. Recent theories suggested that an imbalance in the adjustment of the relative precision of the sensory stimuli and prior could explain behavioral symptoms of ASD (Brock 2012; Pellicano and Burr 2012; Lawson et al. 2014; Van de Cruys et al. 2014; Palmer et al. 2017). The very first theory suggested a decreased prior weight on perception in ASD (Pellicano and Burr 2012). Van de Cruys and colleagues pertinently underlined that any full account of ASD had to take into account not only the nature of priors, but also how priors were learnt and dynamically adjusted in changing contexts (Van de Cruys et al. 2013). As clear empirical evidence was missing, we tested whether perception in ASD could be explained by these hypotheses. Precisely, we aimed at assessing atypical sensory sensitivity, atypical spontaneous choice of a learning strategy, mechanisms of prior construction and adjustment, as well as their neurophysiological and neurobiological underpinnings. Experiments were performed with adults with or without ASD, and included questionnaires, behavioral experiments, computational modelling, functional magnetic resonance imaging, and magnetic resonance spectroscopy.

We first characterized sensory sensitivity and atypical learning style in complex tasks, in relationship to these theories. As foreseen, questionnaires showed that sensory sensitivity is heightened in people with ASD or with high autistic traits, and testimonies suggested that atypical sensitivity is highly dependent on the predictability of the environment. The study of learning-styles in ASD showed a lower tendency to interpolate between stimuli to form abstract categories, in subjects with ASD, despite intact abilities to categorize. This tendency could not be accounted for by visual hypersensitivity, therefore probably reflecting a deeper mechanism of peculiar perceptual learning. The enhanced sensitivity and impaired use of generalization were in line with atypical process of sensory information and prior knowledge.

At a lower level, one of the main questions consisted in determining whether individuals with ASD could implicitly build up priors, as this ability had been questioned in the first theoretical article (Pellicano and Burr 2012). The overall results showed that people with ASD were able to build up priors, and even strong priors, at least in the context of our tactile task, where only one feature had to be encoded (i.e. frequency). We further investigated whether participants were able to adjust their priors in changing environments.

We found that the ASD group had more difficulties to adjust their priors than NT in a changing environment. The ASD group managed to adjust the prior, but did it with a slower dynamic. Contrary to NT, the ASD group did not flexibly adjust the weight of prior information on perception depending on the nature of the context. This result suggests that the precision of the prediction error was not adjusted to enable the fast learning of new regularities linked to this contextual change.

Importantly, perceptual decisions influenced by prior knowledge recruited distinct neural networks in NT and ASD groups: the ACC and cerebellum in NT, and the prefrontal and inferior parietal lobe in ASD. The prediction error involved a similar network in both groups, with an increased modulation of the activity of the IFG by the size of the prediction error in NT, as compared to ASD. Finally, prior weight on perceptual decision was modulated by a glutamate/GABA ratio across NT subjects, but not across ASD subjects. GABA concentration in the somatosensory cortex predicted tactile hypersensitivity in ASD only. These results suggest that perceptual inference and sensitivity would rely on a different neurotransmitter regulation in ASD.

## *2. Atypical perception and learning at the behavioral level*

### *Prior construction and adjustment in ASD*

#### ***Reduced generalization in complex situation (Study II)***

The ASD group had a reduced tendency to use the learning strategy consisting in interpolating between stimuli, to categorize stimuli based on the main shared feature. Each stimulus presented with many details, which could be considered as noise, whereas the main feature represented a statistical regularity to learn. For this kind of complex task, we can hypothesize that people with ASD stored each example precisely, encoding noise, and often ignoring the underlying regularities. The lookup table (LUT) learning style consists in storing each stimulus into memory without compressing information, which can be very demanding and prone to saturation if the number of example increases. Encoding each example with narrow tuning functions is useful to reduce interference between nearby inputs, but does not generalize well (Qian and Lipkin 2011). In the LUT style, the too precise tuning functions of each stimulus can be seen as a too precise encoding of sensory information. We can hypothesize that in ASD, details would be encoded precisely in lower levels of the hierarchy, but at higher levels, the too high weight of this noise might prevent them from building abstract representations. For complex tasks (like Study II) where several features of the stimuli could be encoded, participants with ASD had difficulties getting these high-level priors. However, when the task was simplified, i.e., they were asked to only pay attention to the orientation of the stimuli, they were perfectly able to form abstract categories of stimuli. Interestingly, two previous studies showed that depending on the instructions given, the abilities of children with ASD differ (Koldewyn et al. 2013; Van der Hallen et al. 2016). Indeed, in visual tasks, they showed intact abilities with explicit instructions but decreased abilities with implicit instructions, suggesting a disinclination but not a disability in global processing in ASD. Besides, the literature on generalization or categorization in ASD report quite inconsistent results, showing either abilities to categorize that are similar or impaired compared to controls (Church et al. 2010; Vladusich et al. 2010; Gastgeb et al. 2012). Here, we showed that participants with ASD were able to categorize, but did not do it spontaneously. Hence, the diversity of the results on categorization might be due to the difference in task complexity and instructions between studies.

Our results showing a decreased spontaneous generalization in ASD are consistent with the reduced generalization theory (Plaisted 2001). There are also in line with the idea of predictions being overfitted with noise (Van de Cruys et al. 2013), and of course with the bias toward a reduced use of the INT learning strategy in favor of the LUT one (Qian and Lipkin 2011).

Poor regularity learning with decreased INT style and increased LUT style would be associated with poor learning of relationships that are context dependent, poor prediction and anticipation, frequent surprises, restricted interests, resistance to change, sensory overload, hypersensitivity, weak adaptation, superior and inferior performance on simple and complex tasks (see Qian and Lipkin 2011 for a review). Having difficulties to generalize and categorize in complex situations would highly impair social interaction understanding. Indeed, social interactions are complex, noisy, flexible, and context-dependent.

With the LUT style, a strategy to cope with complex situations would be to “*follow rigidly the memory entry that best matches the current situation as a script*” (Qian and Lipkin 2011). This strategy was spontaneously described by participant S.K. who explained that he had learnt lists of smiles/situations, almost by rote. This is also reflected by the testimony of T. Grandin who explained “*When I encounter a new social situation, I have to search my memory for a similar experience that I can use as a model for my next action. I have a very difficult time when I am confronted with unexpected social surprises. For common social interactions with clients I use preprogrammed, prerehearsed responses. Everything is done with logic*” (Grandin 1997).

### ***Implicit prior learning and adjustment in ambiguous contexts (Study III)***

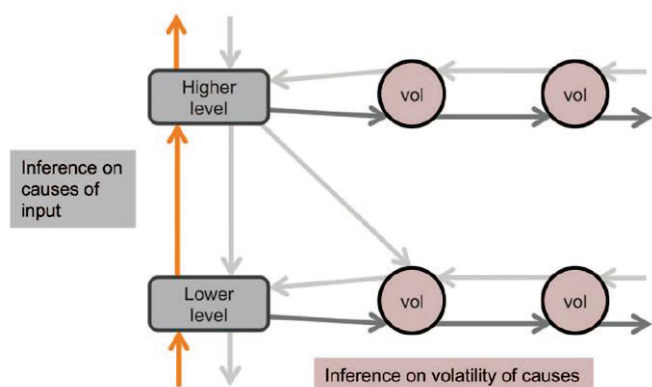
We studied implicit prior learning through the time-order effect in two alternative forced choice perceptual tasks. We showed that adults with ASD were able to build up a prior, and that this prior influenced their perception. This first result provides empirical evidence opposed to the hypothesis that people with ASD would have uniformly weak priors (Pellicano and Burr 2012). Particularly, the influence of these priors in a stable learning context was greater in ASD than NT, suggesting a high precision of these priors. Hence, in this tasks where only one feature (i.e. frequency) needed to be encoded, people with ASD built up very strong priors. Interestingly, it was suggested that individuals with ASD could have very strong predictions on what to expect in stable contexts, but these highly precise predictions would almost never be applicable (Van de Cruys et al. 2013). Too precise predictions would be associated with strong prediction errors, as sensory inputs would never perfectly match

predictions. The testimony of one of the participants with ASD fit the idea of precise priors and reduced ability to adjust them: « *Once I have built up a clear image about what to do, or what is going to happen next, and that somebody changes the program, it devastates me, and I need time to try to get adapted to it* » (Participant I.S diagnosed with ASD, Appendix 2).

It would also result in predictions that could be less flexibly adjusted. Indeed, we found a reduced dynamic in the adjustment of priors in a changing context. This is consistent with the strongly reduced adaptation that we observed in the same ASD participants, suggesting that priors are learnt more slowly, and thus influence perception less in short time lapses. A slower prior adjustment in ASD suggests a lower learning rate, which is in contradiction with previous Bayesian accounts of ASD which suggest that highly precise predictions errors would be associated with an increased prior update (Brock 2012; Pellicano and Burr 2012; Lawson et al. 2014). Yet, a lower learning rate is consistent with the finding that adults with ASD poorly learn statistical regularities in a changing context (D’Cruz et al. 2013; Robic et al. 2014). A behavioral study also showed poor learning in ASD when the context changed, due to an over-specificity of the previously learnt context (Harris et al. 2015). Indeed, participants with ASD had a slower learning rate than NT when they had to learn a new condition following prior learning. This idea of a too specific learning followed by slower learning rate in changing contexts is fully consistent with the idea that individuals with ASD could build up very strong priors and would have difficulties to adjust these priors to new contexts.

The group difference in the dynamic of prior adjustment also underlines the necessity to take into account the temporal evolution of the environment, in other words its volatility. A general and biologically plausible Bayesian account of volatility has been proposed with the so-called Hierarchical Gaussian filter (HGF) (Mathys et al. 2014). This is particularly important for

learning and decision-making tasks with volatile statistical structures. In this view, predictions and prediction errors are considered within a *causal hierarchy* but also in a *volatility hierarchy* (Figure 37). To fully understand perceptual inference in ASD, the importance of higher order expectations on the volatility of the environment has been underlined in two



**Figure 37 : Model of predictive processing including causal and volatility hierarchies**  
(Palmer et al. 2017)

recent reviews (Van de Cruys et al. 2016; Palmer et al. 2017). Expectations on volatility will flexibly tune the precision of priors or prediction errors in the causal hierarchy. Indeed, contexts are associated with certain expectations on the kind of sensory information, but also with expectations on the type of variability we can expect (Van de Cruys et al. 2016).

Our results suggest that, contrary to a weak prior assumption that might apply to the causal hierarchy, a strong prior on the inflexibility of the environment in the volatility hierarchy may be at play in ASD. As observed, this inflexibility in adjusting priors would indeed render learning or adaptation slower (weaker) in ASD and would reduce modulations due to context changes.

### ***Conclusions based on behavioral findings (studies I, II, and III)***

Our experimental results showed that the mechanisms underlying perceptual inference and learning in ASD could not be simply explained by weak priors or high sensory precision, but by a more complicated picture.

People with ASD were able to build up a prior when only one feature needed to be encoded (i.e. orientation in Study II after explicit instructions, and frequency in Study III). This is consistent with the idea that “*extracting a mean estimate [...] should not pose a problem in ASD when the display does not include noise that should be weighted differently than the rest of the input*” (Van de Cruys et al. 2016). The ASD group might have overfitted sensory inputs, leading to narrow priors in a stable context (Study III, experiment 1) and to detail-oriented learning strategies (Study II, LUT learning style). However, in more complex contexts they might have not been able to build up priors allowing generalization (Study II, reduced use of the INT learning style).

Moreover, individuals with ASD might expect the environment to be highly stable (low volatility). Together with a high precision of low-level priors, this strong expectation about the inflexibility of the environment would be associated with a reduced ability to adjust priors in changing contexts (Study III, experiment 2). A decreased learning rate to update priors would also be consistent with the reduced prior influence in short time lapse, as seen with the reduced adaptation of the ASD group (Study III).

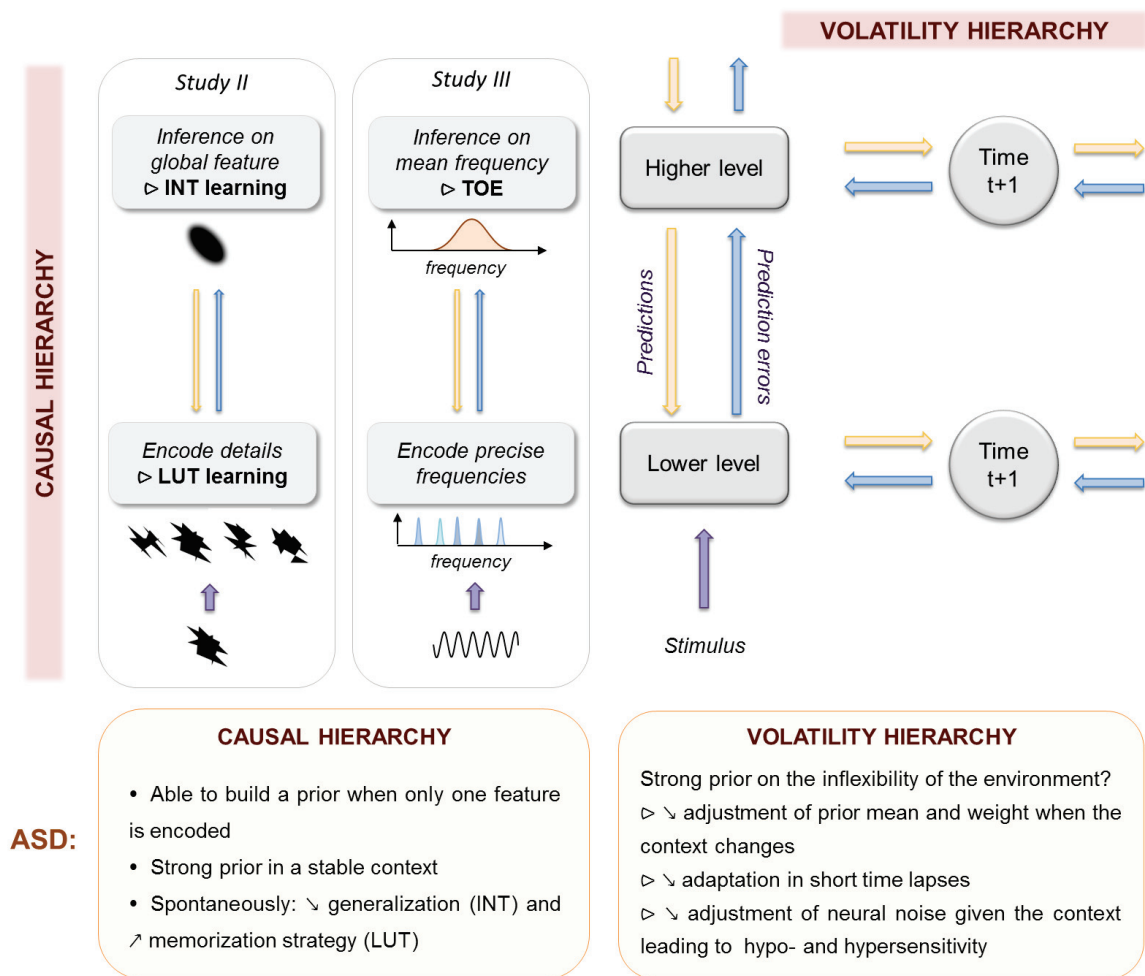
Priors on the volatility of the environment adjust the relative weight of ascending prediction errors, and so, adjust the level of neural noise (Van de Cruys et al. 2016). Hence, in ASD, sensory information encoding would not be given a high or low level of sensory noise *per se* (as suggested by Simmons et al. 2009; Davis and Plaisted-Grant 2015), but would depend on the context. This could explain the presence of both hypersensitivity and



hyposensitivity in ASD (Study I) and the fact that hypersensitivity would be highly related to unexpectedness (Appendix I).

To sum up, people with ASD would have low-level hyper-priors and high-level hypo-priors in the causal hierarchy, and strong priors on the inflexibility of the environment in the volatility hierarchy leading to strong prediction error but reduced adjustment of priors following changes in context. The main results and conclusions are summarized in Figure 38.

**Figure 38 : Summary of the behavioral results and hypotheses in ASD**



## Perspectives

### Developing dynamic models

With dynamic models like the HGF (Mathys et al. 2014), we could more precisely characterize the prior adjustment and prediction error precision at each trial, along with environmental changes, within the causal hierarchy. We could also estimate in-built priors about the volatility of the environment, in the volatility hierarchy. We would expect the ASD

group to have a strong prior (high precision) assuming the inflexibility of the environment. Hence, changes in the environment should elicit strong prediction error, and should not lead to the immediate update of the priors.

### ***Manipulating the precision of priors***

We could experimentally induce other types of modulations of prior precision in order to better understand their tuning and interplay with the precision attributed to the sensory input. In the context of a tactile TOE task, prior precision can be further modified by changing either the frequency range or the frequency distribution. For instance, prior precision could be increased by restricting the range of delivered frequencies. The condition with a precise prior (e.g. frequencies ranging from 25 to 35Hz) could be compared with a looser prior (e.g. frequencies ranging from 15 to 45Hz). Or slightly differently, the delivered frequencies could have a uniform distribution leading to a relatively flat prior, or a Gaussian distribution (e.g. lower occurrence of 25Hz and 35Hz than 30Hz) leading to a more precise prior.

In ASD, if priors fit the sensory data more precisely than in NT, we could expect these changes in prior precision to have a greater effect on the TOE in ASD than NT. It would help understanding how priors are computed from sensory inputs in ASD. Besides, we could assess confidence in their perceptual decision under different levels of prior precision, by asking the participants to rate their confidence on their decision at each trial. Interestingly, performance and confidence judgments are dissociable and it remains quite unclear how observers produce such metacognitive evaluations in ambiguous contexts (de Gardelle and Mamassian 2015; Pouget et al. 2016).

### ***Manipulating the precision of sensory information***

The precision of the incoming sensory input could also be manipulated, but modifying the sensory input will also affect prior precision. Overall, decreasing sensory precision should increase the TOE and reduce the accuracy. In the context of a two alternative forced choice perceptual task, sensory precision could be decreased by adding noise to the delivered stimulation or by reducing the time of exposure. Such manipulations have been already tested in healthy adults and yielded an increased time-order effect (Ashourian and Loewenstein 2011; Karim et al. 2013). As adding noise to tactile frequencies is not trivial, we explored such manipulations in the visual domain, in a pilot study with control participants only (Appendix 2). However, our preliminary results showed that the noise added in the stimuli was neither sufficient to significantly decrease accuracy, nor to affect the time-order effect.

In ASD, if the confidence given to sensory evidence is increased (Brock 2012), we could expect the ASD group to be more affected by changes in sensory precision. Previous studies indeed showed that adding noise in sensory inputs impaired global motion perception, especially for participants with ASD (Milne et al. 2002). Quite unexpectedly, a recent motion coherence study showed that children with ASD could tolerate more variability than controls when judging mean direction of dots, in a context where all dots were directed toward the same side but with a certain standard deviation (Manning et al. 2015). In this context where all dots were informative, the indiscriminate weighting of all dots directions to estimate a mean could have been done (Van de Cruys et al. 2016). This would be in line with the idea of an atypical weighting of sensory relevant information from random noise (Van de Cruys et al. 2016).

### ***Manipulating the volatility of the environment***

In this thesis, we focused on prior construction and update in contexts containing relatively few changes. A complementary approach would consist in studying perceptual inference and learning in more unstable contexts, where the predictability of the context would fluctuate (e.g. like in Robic et al. 2014; Manning et al. 2016). This result supports the idea that the precision of the prediction error would decrease in stable (predictable) contexts (Palmer et al. 2017). In ASD, a high and inflexible precision of the prediction error should be seen by a stronger deviance response, but the difference of responses between the predictable and unpredictable contexts within group should be diminished as compared to NT. Besides, a decision-making task showed that adults with ASD had difficulties extracting the underlying statistical rules useful to make correct decisions in unstable contexts only (Robic et al. 2014). Indeed, adults with ASD managed to perform the decision-making task in the stable context, but were impaired when the statistical rules changed. This result is in line with the idea that individuals with ASD have flexibility problems, and rather expect that the environment will not change.

### ***Exploring perceptual inference in other contexts***

The time-order tasks presented in this thesis were based on the tactile modality, and we can expect the results to be similar in every other sensory modality. It would also be informative to study the TOE in multi-sensory contexts (i.e. more ecological), where the sensory precision of the different stimulation sources should be weighted differently, in order to allow optimal inference on the feature of interest.

Besides, linking difficulties in social contexts to atypical perceptual inference could help understanding whether social impairments are truly domain-specific or whether they could be explained by lower-level cognitive processes such as abnormal predictions. The decision-making task cited above (Robic et al. 2014) showed that accurate choices were decreased when the unpredictability of the context increased, and that this decrease in accuracy was more pronounced in social context than in non-social context. However, social stimuli affected less accuracy than unpredictability did. Finally, a recent MMN study suggested that some perceptual processes might be specifically altered by social stimuli (Lortie et al. 2017).

### ***Understanding perceptual inference in other populations with ASD***

This thesis work was restricted to the study of adults with ASD without intellectual deficiency (i.e. former diagnosis of “Asperger syndrome” or “high functioning autism” in the DSM IV). Testing Bayesian brain theories of ASD in populations with intellectual deficiency, as well as in children and adolescents, would help getting a more comprehensive explanation of ASD. The time-order effect has not been tested in children with ASD, and simple tasks like those involving the comparison of length of bars (Ashourian and Loewenstein 2011) could be quite easily adapted to children. To study these processes in even younger children with ASD, or in subjects with ASD presenting with intellectual deficiency, passive paradigms could be used. These paradigms could include eye-tracking measuring increased pupil dilation as a sign of prediction error (Preuschoff et al. 2011), or MMN paradigms. For instance, an interesting MMN study showed that when the predictability of the context increased, the deviance response decreased in control participants (Lecaignard et al. 2015). This kind of passive paradigm could be tested in ASD to assess how prediction errors or predictions are modulated by the unpredictability of the context.

### *3. Atypical perception and learning at the brain network level*

#### *Neural correlates*

##### ***Prediction error influence on brain activity***

In our fMRI study, we found that the size of the prediction error on the first stimulus modulated the activity of a brain network encompassing the somatosensory cortices, the prefrontal and orbitofrontal cortices, the inferior parietal lobe, the anterior insula and the inferior temporal cortex. This network was shared by the two groups, suggesting that these regions play a key role in perceptual inference. The only group difference (on prediction error) was a weaker modulation of the orbital and triangular parts of the IFG by prediction error in the ASD group. This is consistent with a reduced flexibility in the adjustment of prediction error precision in ASD. Nonetheless, note that the activity of the rest of the neural network followed the same modulation in both groups, suggesting that there is still some flexible modulation depending on the size of the prediction error in ASD. The main group difference might be in the dynamic adjustment of priors and in the modulation of the prediction error precision under different levels of uncertainty. These aspects will be studied using the analyses suggested in the perspective section below.

Interestingly, in an fMRI study investigating different sizes of visual prediction error, Sherman et al. (2016) revealed exactly the same network as we did (apart from the anterior insula, and somatosensory cortices). Using connectivity analyses enabled them to evidence that the orbitofrontal cortex (OFC) represented top-down prior information. The OFC was connected to the IFG, a region which mapped the discrepancy between expectations and perceptual choices (Sherman et al. 2016). Besides, several studies showed that the anterior insula plays a role in prediction error encoding. Indeed, a study with stereotactically implanted electrodes in humans revealed that the anterior insula rapidly conveys error signal to the dorsomedial prefrontal cortex (Bastin et al. 2017). In addition, a dynamic causal modelling study showed that unexpected tactile stimuli increased the strength of forward connections from somatosensory cortex to the anterior insula and that this region showed increased backward connectivity to the somatosensory cortex, therefore suggesting that the anterior insula coordinates hierarchical processing of tactile prediction errors (Allen et al. 2016).

### ***Prior influence on brain activity during decision-making***

In our fMRI study, the parametric modulator P2 measured the subjective difficulty in comparing the two stimuli. The objective difficulty was the same in every trial, but the percept of the first stimulus was greatly modified by the prior, resulting in several degrees of difficulty. Depending on the difference between the sensory input and the prior, and the order of presentation of the two stimuli, we estimated five levels of difficulty in our task.

In NT, increased subjective difficulty (P2) was associated with increased activity in the ACC, and this modulation was stronger in the NT than in the ASD group. The ACC plays a key role in decision-making under uncertainty, in monitoring conflict and in encoding prediction error (Ide et al. 2013). Importantly, optimal estimates of volatility and learning rates were reflected by ACC activity in a decision-making task under several levels of uncertainty (Behrens et al. 2007). Interestingly, the ACC has an action on norepinephrine modulation because it innervates the locus coeruleus (Aston-Jones and Cohen 2005). The ACC also has the particularity to contain Von Economo neurons, which might be involved in the fast intuitive assessment of ambiguous situations (Allman et al. 2005). Allman and colleagues suggested that autistic symptoms could be due to abnormal development of Von Economo neurons. Histopathology studies showed inconclusive results on these neurons in ASD, with increased or decreased density, decreased size, and different patterns depending on the age group (Simms et al. 2009; Uppal et al. 2014).

In addition, increased subjective difficulty was also associated with increased activity of the cerebellum in NT, a region involved in prediction update and sensory prediction error encoding (Courchesne and Allen 1997; Dreher and Grafman 2002; Synofzik et al. 2008; Leggio and Molinari 2015). Remarkably, a great number of structural abnormalities were found in the cerebellum of individuals with ASD (Fatemi et al. 2012), such as decreased density of Purkinje cells (Ritvo et al. 1986; Kemper and Bauman 1993; Bailey et al. 1998; Amaral et al. 2008), and decreased production of glutamate decarboxylase, the enzyme converting glutamate into GABA (Yip et al. 2007). A recent magnetic resonance spectroscopy study showed hyperglutamatergic and hypoGABAergic alterations in the cerebellum of individuals with ASD, as well as hypoGABAergic alterations in the ACC (Ito et al. 2017). As the cerebellum plays an important role in predictive processing and since its neurobiology shows alterations in ASD, it was pointed out as a potential key region to explain impaired predictive abilities in ASD (Sinha et al. 2014; Leggio and Molinari 2015).

In the ASD group, increased subjective difficulty was associated with increased activity in the IFG and inferior parietal lobe, and this modulation was significantly stronger than in NT. These two regions have been related to prediction error and prior encoding (see Theoretical background II.3). A recent fMRI study showed that subjective confidence increased with prior expectations, and that this relationship was associated with increased IFG activity (Sherman et al. 2016). We could interpret our results as a stronger influence of priors on decision, however, a stronger prior influence should be associated with an increased amplitude of the TOE, which was not observed here. Interestingly, Gomot et al. (2008) showed that novelty detection was associated with a stronger activation of the prefrontal cortex (including the IFG) and inferior parietal lobe in ASD, as compared to NT. In their study, increased activity in these regions could be interpreted as increased prediction error.

### ***The IFG: a potential key region for priors***

In perceptual inference tasks, the inferior frontal gyrus (IFG) has often been pointed out as an important brain region for contextual processing and high-level priors (Preuschhof et al. 2010; Spitzer et al. 2010; Auksztulewicz et al. 2011; d’Acremont et al. 2013; Romo and de Lafuente 2013; Sanchez 2014; Barredo et al. 2016). In our task, this region was also found to be modulated by the prediction error, with a greater modulation in the NT group, and by the subjective difficulty in the ASD group.

Remarkably, a large variety of studies, not specifically targeting perceptual inference, suggested that the IFG could be related to prior knowledge and context dependence. For instance, the IFG was involved in internal timing mechanisms influenced by prior context (Jantzen et al. 2004), in action comprehension influenced by prior knowledge (Möttönen et al. 2016), in the prediction of movement goals (Ondobaka et al. 2015), in contextual modulation of expectations with visual ambiguous figures (Ishizu 2013), and in memory updating with new memories (Kuhl et al. 2012). In terms of functional connectivity, proactive control for anticipatory mechanisms originated in the IFG (Di Russo et al. 2016), and this region also had top-down influence on memory retrieval (Barredo et al. 2016). Besides, the IFG could be related to more abstract priors. For instance, a study where young children were asked to indicate the food they would prefer to eat and to project the food their mothers would choose for them showed that the IFG encoded the projected mother’s choice, whereas the orbital part of the superior frontal gyrus (SFG) encoded the child’s decision (Lim et al. 2016). When the children indicated their own choice, the IFG influenced the SFG activity. On a more abstract

level, we could interpret that the IFG activity reflected the encoded mothers' priors, influencing their decisions.

Interestingly, the anatomical development of the IFG, particularly of the opercular part, differs in ASD individuals as compared to controls (Zielinski et al. 2014). The atypical developmental trajectory of the IFG is characterized by a reduced cortical thickness in adults with ASD (Zielinski et al. 2014), which might impact its function. A segmentation of this region in our group of subjects could inform on the potential links between the grey matter volume of the IFG and functional or behavioral results.

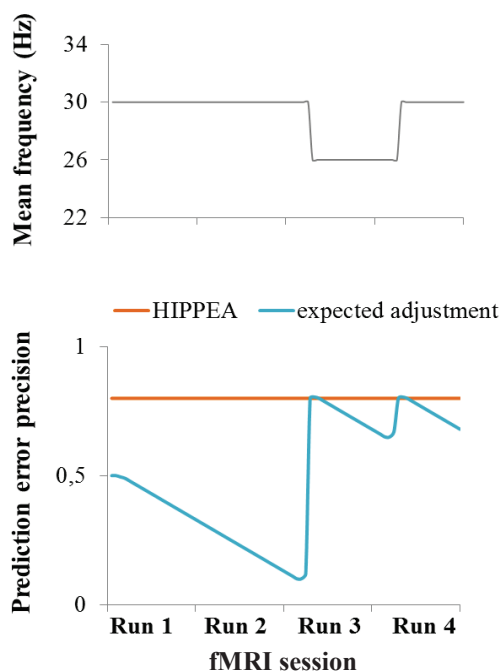
## Perspectives

### *Psychophysiological modelling of our fMRI data*

- *Characterizing inference and learning with computational models of perceptual decision-making*

Dynamic computational models applied to our fMRI study could capture the effect of contextual changes through changes in prior and prediction error precisions over trials. It would also enable to assess beliefs about the volatility of the environment. Hence, we could target the brain regions whose activities follow the changes in prediction error precision and prior adjustment. In runs 1 and 2 (when the context remains stable), we can expect the precision of the prediction error to gradually decrease (Palmer et al. 2017). At the beginning of runs 3 and 4 (when the context changes), we can expect the precision of the prediction error to be attributed a higher weight. Figure 39 shows a schematic representation of the expected evolution of the prediction error precision. If the precision of the prediction error is strictly high and inflexible in ASD, we could expect no evolution, as depicted by the orange line. A more realistic pattern for the ASD individuals would be a pattern in between the blue and orange profiles.

**Figure 39 : Schematic representation of the hypothesized evolution of the prediction error precision depending on context changes**

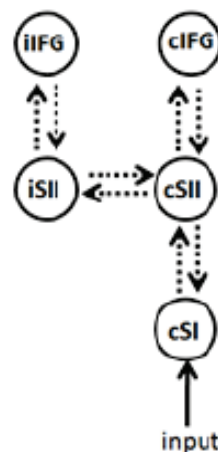




• *Characterizing effective connectivity using dynamic causal modeling*

Dynamic causal modeling enables to determine how changes in experimental parameters influence coupling between brain regions. It is a hypothesis-driven method which can infer directionality of context-dependent interactions between brain regions (Friston et al. 2003). Using DCM, we should be able to specifically study prediction errors represented by bottom-up connections, and predictions represented by top-down connections, as well as their modulation depending on the changes in the experimental design.

In a tactile time-order task including changes in contexts, Sanchez 2014 used DCM to identify the network presented in Figure 40. Tactile inputs passed from the contralateral S1 to bilateral S2, and then to bilateral IFG (opercular part), with bidirectional connections.



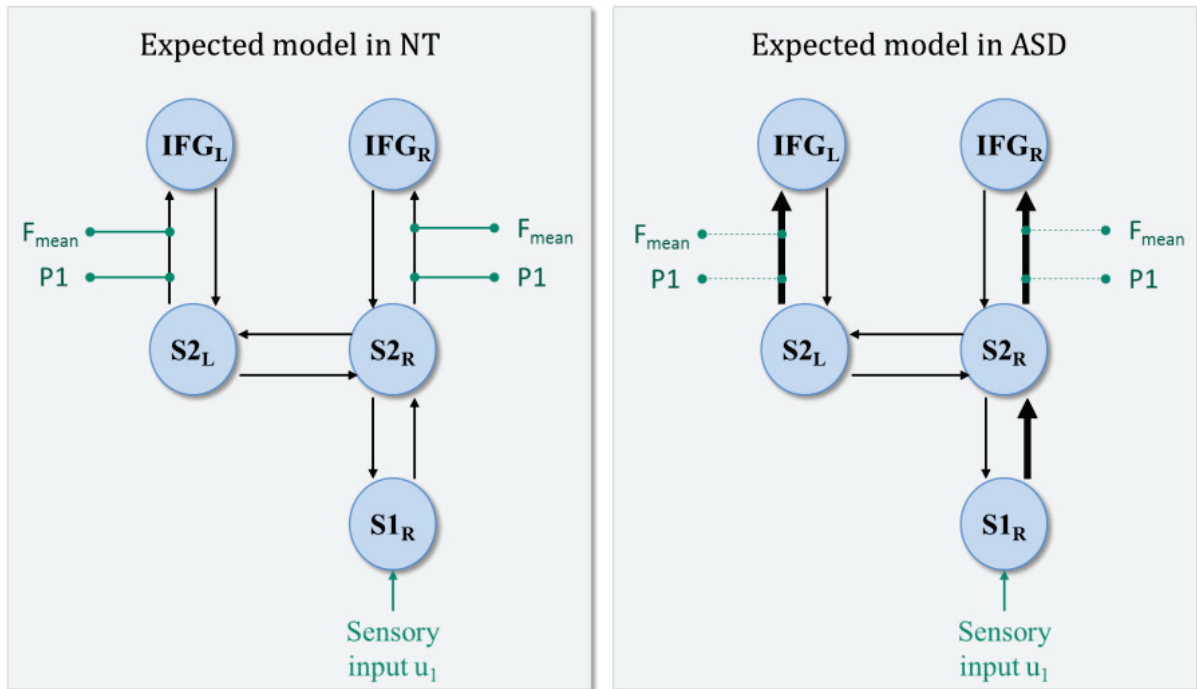
**Figure 40 : DCM results of a MEG study with control subjects**

*This network models connections during a tactile task eliciting a time-order effect. (Sanchez 2014)*

In our fMRI study, DCM could help determining whether participants with ASD have a high and inflexible precision of the prediction errors, which would be reflected by stronger and context-independent bottom-up connections. Interestingly, an MEG study found increased feedforward connectivity in the somatosensory cortex of ASD participants, suggesting increased prediction error precision in the early steps of tactile perception (Khan et al. 2015). The effect of the modulation by the global context (average frequency of the session), and by the parametric modulator P1 (difference between the frequencies of the first stimulation and of the prior) should be smaller on the bottom-up connections in the ASD group, as compared to the NT. No contextual modulation of the connection strength could be seen as marker of decreased plasticity in ASD. Figure 41 illustrates the expected DCM results of our fMRI study, with a simplified brain network.

A complexified network could include (1) the ACC, whose connection with the IFG would be modulated by P2, (2) the inferior parietal lobe, whose connection with S2 would be modulated by P1, (3) the orbitofrontal cortex, whose connection with the IFG would be modulated by P2 (Sherman et al. 2016), and (4) the anterior insula, whose connection with S2 would be modulated by P1 (Allen et al. 2016).

**Figure 41 : Expected DCM results in the fMRI study**



*P1 reflects the size of the prediction error on the first tactile stimulation (difference between the prior frequency and the received frequency).*

*Larger arrows correspond to increased connection strength, i.e., increased weight of the ascending prediction errors in the ASD group.*

*Dash lines indicate reduced effects of these modulators on the connection strength.*

*$F_{mean}$ : average frequency of the context. Context changes in runs 3 and 4 should modulate these connections.*

## 4. *Atypical perception and learning at the molecular level*

### *Neuromodulation in perceptual inference*

The neurotransmitters presented as key candidates for the control of prediction error are glutamate, GABA, acetylcholine (Ach) and norepinephrine (NE) (Yu and Dayan 2005; Friston 2010; Moran et al. 2013; Lawson et al. 2014; Van de Cruys et al. 2014). Lawson and colleagues suggested that these neuromodulators could take action on different timings: glutamate and GABA could modulate short temporal contexts, whereas Ach and NE could modulate more enduring contextual aspects (Lawson et al. 2014).

Our results suggest that the glutamate/GABA neuromodulation impacts perceptual inference differently in NT and ASD. Indeed, this ratio predicted the extent to which NT subjects were biased toward priors, suggesting that the suppressive field gain could explain some modulation in prior weight (Rosenberg et al. 2015). In contrast, we found no relationship between this ratio and prior influence in participants with ASD. In both groups, GABA increase was associated with decreased variability in tactile sensation, suggesting that GABA could tune sensory precision between individuals. Finally, in ASD participants only, increases in self-reported hypersensitivity were specifically associated with increased GABA concentration in the somatosensory cortex. Hence, GABAergic modulation could contribute to the atypical sensory sensitivity of people with ASD.

The dynamic adjustment of priors would involve Ach and NE, encoding expected uncertainty and unexpected uncertainty, respectively (Yu and Dayan 2005). Higher Ach availability was associated with more precise bottom-up prediction errors (Moran et al. 2013), suggesting that HIPPEA should be associated with high Ach concentrations. In the context of our time-order task, Ach should weight prediction errors differently as a function of the difference between the received stimulus and the prior, as it can be seen as a form of expected uncertainty. In other words, for a prior mean at 30Hz, Ach should increase the prediction error precision to a greater extent for stimulations at 25Hz than 29Hz. Hence, cholinergic modulation should be associated with the parametric modulator P1 of our fMRI task. Besides, NE modulation would reflect the monitoring of contextual changes as encountered at the beginning of runs 3 and 4. NE modulations could then be associated with different beliefs about the volatility of the environment.

## *Perspectives*

### ***Tracking pupil dilation to assess NE neuromodulation***

As NE induces pupil dilation, measuring changes in pupil size using eye-tracking can be a way to assess NE modulation (Langham et al. 1971; Bylund and Chacko 1999). Indeed, non-luminance mediated pupil dilation follows the activity of the NE locus coeruleus (Aston-Jones and Cohen 2005). Remarkably, the learning rate can be directly tracked by changes in pupil size (Nassar et al. 2012). In addition, pupil dilation signals errors in judging uncertainty, suggesting that NE modulates prediction errors in contexts of uncertainty (Preuschoff et al. 2011). Changes in pupil size also reflect biased perceptual decisions in uncertain contexts (de Gee et al. 2014).

In our fMRI study, pupil size was measured across trials using eye-tracking, in order to relate increased pupil dilation to unexpected context changes. The pupillometry data have not been fully analyzed yet. We hypothesized that in NT subjects, pupil size should increase when the context is changing (runs 3 and 4), while in ASD, this context change should elicit a stronger increase in pupil size than in NT if subjects have a strong belief on the inflexibility of the context.

### ***Using pharmacological agents to target specific neuromodulators***

The role of neuromodulators on perception can also be assessed using pharmacological agents increasing or decreasing their availability. In their EEG study, Moran and colleagues found increased MMN responses following galantamine administration, a substance increasing Ach availability in the synapse (Moran et al. 2013). Precisely, increased Ach availability boosted the gain of prediction errors and reduced adaptation to surprising stimuli in sensory cortices (Moran et al. 2013). In ASD, the atypical MMN responses (Gomot et al. 2002; Ferri et al. 2003; Kujala et al. 2007; Gomot et al. 2011; Cléry et al. 2013; Sokhadze et al. 2016) could be mediated by increased cholinergic action. Hence, using an agent transiently reducing the availability in Ach might lead to similar MMN responses in control and ASD participants. Paradoxically, a study in a mouse model of ASD showed that increasing Ach levels (with acetylcholinesterase inhibitors) in the caudate nucleus reduced cognitive rigidity and improved social interactions (Karvat and Kimchi 2013), therefore suggesting decreased cholinergic modulation in ASD.

Given our MRS results, it would be of interest to test perceptual inference in ASD, after administration of an agent modulating GABA availability. Precisely, we could measure

time-order effect in groups of children having followed or not a treatment with bumetanide, which is a diuretic increasing GABAergic inhibitory action, and improving core symptoms of ASD (Lemonnier et al. 2017). Measuring low-level perception and learning could contribute to assess the efficacy of this treatment.

### ***Using PET to estimate acetylcholine and norepinephrine concentrations***

Ach and NE levels could be assessed in ASD and NT individuals using positron emission tomography (PET), particularly in the basal forebrain and locus coeruleus, which are the main sources of Ach and NE. Available PET radiotracers include ligands of NE transporter (Ding et al. 2006; Moriguchi et al. 2016), Ach transporter (Kitamura et al. 2016), Ach nicotinic receptor (Wong et al. 2013; Hillmer et al. 2016), and Ach muscarinic receptor (Buitter et al. 2013). Hence, using PET would allow *in vivo* measurements of the Ach and NE which are supposed to play a key role in prediction error precision modulation under different levels of uncertainty, and which cannot be measured using MR spectroscopy.

### ***Using genetics to track variants related to these neuromodulators***

As Ach, NE, GABAergic and glutamatergic basal concentrations depend on their level of translation, it would be very informative to link observed behaviors to these neurotransmitters. To do so, we initiated an exploratory study with a geneticist who is currently collecting blood samples from ASD participants involved in our fMRI study (six participants have been involved so far). A CGH-array (Comparative Genomic Hybridization microarray) and a DNA microarray will be performed with these blood samples. The CGH-array can identify large chromosomal deletion, duplication or translocation. Although it is unlikely that the CGH-array will evidence such chromosomal abnormalities, it is important to ensure that there are no large genetic abnormalities. The DNA microarray can measure expression levels of more than 400 genes, including genes involved in Ach nicotinic receptor (*Chrna2*, *Chrna4*, *Chrna7*, *Chrn2*), glutamate receptor (*Grin1*, *Grin2a*, *Grin2b*) and GABA receptor (*Gabrd*, *Gabra1*, *Gabrg2*, *Gabrb3*). Mutations or variants in these genes could therefore be related to behavioral measures of perceptual inference or sensitivity, and to MRS measurements. Interestingly, deletion of *Gabrb3* has been associated with tactile hypersensitivity in mice models of ASD (DeLorey et al. 2011).

Future studies should also test the Bayesian brain hypotheses in groups of genetically homogeneous individuals with ASD, in order to get a clearer picture of the interaction between genetics and behavioral symptoms.

## 5. *General perspectives*

### *Current challenges for ASD diagnosis and care*

#### ***Diagnosis***

In a recent review, Haker et al. (2016) explained the four main challenges of ASD diagnosis. They suggested that the Bayesian approach should be used to develop clinically useful tests in ASD. The large heterogeneity of the symptoms makes ASD diagnosis harder, and objective and quantitative assessment tools are currently lacking. The first challenge is to find quick and easy diagnosis tests which could be performed by non-specialists to favor early diagnoses (Haker et al. 2016). The second challenge is to accurately diagnose individuals with mild forms of ASD, as (1) standard tests are less sensitive to these forms, (2) only subtle signs are visible, (3) symptoms are often hidden by compensation strategies for short time periods, (4) individuals with ASD might experience difficulties to describe their particularities, (5) ASD might be overshadowed by other comorbidities such as depression. The third challenge is to diagnose very young children to optimize care and outcomes. Finally, the fourth challenge is the assessment of intelligence in ASD patients without spoken language, as current assessment would underestimate intelligence in these patients.

#### ***Care***

The currently available treatments for children with ASD mostly rely on behavioral interventions. These interventions usually show improvements in social interactions, especially when the intervention is intense and started at a young age (Lovaas 1987; Rogers et al. 2012; Weitlauf et al. 2014; McPheeters et al. 2016; Linstead et al. 2017). Behavioral interventions are often supplemented with rehabilitative services such as speech, physical or occupational therapies, as well as social skills training and counseling (Choueiri and Zimmerman 2017). These interventions mostly focus on the development of language and social skills in children with ASD.

Haker and colleagues described the main treatment challenges, as follows (Haker et al. 2016). First, there is a need for efficient behavioral interventions fostering socioemotional development in adults with severe forms of ASD. Second, symptoms such as sensory hypersensitivity, detail-dominated perception, or need for sameness and routines should also be treated in adults with milder forms of ASD. Third, psychotherapies of disorders such as depression, which is commonly comorbid in ASD, should be adjusted for patients with ASD.

In addition, a pharmacological therapy approach could be developed using quantitative and individualized pathophysiological approaches.

### *Diagnosis and care perspectives*

Computational psychiatry within the Bayesian brain perspective offers a possibility to contribute to ASD diagnosis and care. Generative models can infer the causes of the observed behavioral and neurophysiological data. The plausibility of several models can be compared using statistical model comparison techniques (such as those used in the Study III) (Stephan and Mathys 2014). Testing low-level perception and learning could be a way to contribute to ASD diagnosis, particularly for people with more discreet high-level symptoms (due to strategies, such as mimicking other's behaviors).

For diagnosis, computerized cognitive experiments analyzed with generative models could constitute clinically applicable tests (Haker et al. 2016). These tests would assess the relative contribution of prior and sensory input on perception, or the adjustment of prediction error precision across different context. However, in order to construct such tests, we first need to fully understand the perceptual inference processes in ASD, and to find characteristics that are sensitive and specific enough to be clinically applied. Hence, the optimal tests should be specific to ASD, and provided without verbal instructions. Furthermore, the ideal test should not require an extended attention period to include every kind of subjects. It could also rely on eye-tracking measurements to allow measurements in very young children.

Better knowledge on perceptual inference in ASD can also contribute to improve behavioral interventions, by proposing strategies to reduce surprises, or by making the environment more predictable. Our results also highlighted the importance of the context (changing or not) and of the kind of stimuli (complex or simple) in perceptual and learning abilities of people with ASD. Recently, a program has been developed to take into account these difficulties related to predictability in ASD. This program named Coping with Uncertainty in Everyday Situations (CUES) was specifically developed in that aim (Rodgers et al. 2016). It corresponds to a manualized treatment program with eight sessions with parents of autistic children, and it aims at targeting problems due to inflexibility and to propose adapted solutions. This program seems promising, but its efficiency remains to be scientifically evaluated.

Besides, a better understanding of perceptual learning might help defining more optimal conditions for learning at school, for instance. Indeed, we found that learning based

on training examples did not allow adults with ASD to spontaneously interpolate between examples to generalize, but that they were perfectly able to categorize when they were explicitly told to do so. It therefore indicates that providing clear guidance towards a particular strategy could help people with ASD in uncovering underlying rules. Our experiment was performed with adults, and it would be very informative to assess whether these results can be extended to children with ASD.

Furthermore, approaching sensory sensitivity from a computational perspective should help understanding the emergence of both hypersensitivity and hyposensitivity. Optimal living or working contexts could be specified using a fine characterization of sensory sensitivity (e.g., using the GSQ), and of the evolution of this sensitivity with the context and various levels of uncertainty.

The main autistic symptoms should be re-interpreted within the Bayesian brain framework. Importantly, the latter has been extended to encompass action, and is known as active inference (Friston et al. 2010, 2011). It offers the perspective to find core explanations for both perception and motor related symptoms (Palmer et al. 2017). Active inference supposes that prediction error can be minimized by updating priors or by acting on the environment to make it fit priors. Palmer and colleagues suggested that repetitive behaviors in ASD could be understood in terms of the balance between perceptual updating during inference, and action to change the state of the environment (Palmer et al. 2017).



## 6. General conclusion

In this thesis, we characterized perceptual inference and learning using experiences combined with computational models, at the behavioral, neurophysiological and neurobiological levels. We showed that people with ASD were able to compute priors, but that they had difficulties adapting these priors to new contexts, as compared to NT. This decreased flexibility could be interpreted as the result of overconfident priors about the inflexibility of the environment. For more complex tasks, people with ASD tended to interpolate less spontaneously between stimuli in order to form abstract synthetic representations. Yet, they were able to categorize when explicitly asked to do so. Besides, we found that the neural networks involved in perceptual learning were modulated differently in ASD, and that GABA and glutamate modulated differently prior weighting in ASD, as compared to NT. Altogether, these results suggest that the relative precision of prior and sensory inputs could explain atypical perception but also higher level symptoms in ASD, such as social interaction difficulties.

A better understanding of perceptual inference could improve the characterization of ASD. More globally, advances in computational psychiatry could contribute to ASD diagnosis and to the care for people with ASD (Stephan and Mathys 2014). Investigating perceptual inference within the Bayesian framework would also help better characterizing other psychiatric conditions, such as schizophrenia which is also associated with aberrant perceptual inference (e.g. hallucinations) and abnormal beliefs (e.g. delusions) (Fletcher and Frith 2009; Stephan et al. 2016).

As speculated by Haker and colleagues, someday, ASD might be redefined as a “*congenital perceptual inference disorder*” (Haker et al. 2016).

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## REFERENCES

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- Adams WJ, Graf EW, Ernst MO. 2004. Experience can change the “light-from-above” prior. *Nat Neurosci.* 7:1057–1058.
- Allen M, Fardo F, Dietz MJ, Hillebrandt H, Friston KJ, Rees G, Roepstorff A. 2016. Anterior insula coordinates hierarchical processing of tactile mismatch responses. *NeuroImage.* 127:34–43.
- Allman JM, Watson KK, Tetreault NA, Hakeem AY. 2005. Intuition and autism: a possible role for Von Economo neurons. *Trends Cogn Sci.* 9:367–373.
- Amaral DG, Schumann CM, Nordahl CW. 2008. Neuroanatomy of autism. *Trends Neurosci.* 31:137–145.
- Amaral DG, Sinnamon HM. 1977. The locus coeruleus: neurobiology of a central noradrenergic nucleus. *Prog Neurobiol.* 9:147–196.
- American Psychiatric Association. 2013. *Diagnostic and Statistical Manual of Mental Disorders, DSM Library.* American Psychiatric Association.
- Anagnostou E, Taylor MJ. 2011. Review of neuroimaging in autism spectrum disorders: what have we learned and where we go from here. *Mol Autism.* 2:4.
- Ashburner J, Bennett L, Rodger S, Ziviani J. 2013. Understanding the sensory experiences of young people with autism spectrum disorder: a preliminary investigation. *Aust Occup Ther J.* 60:171–180.
- Ashourian P, Loewenstein Y. 2011. Bayesian inference underlies the contraction bias in delayed comparison tasks. *PLoS One.* 6:e19551.
- Asperger, H. 1944. Die “Autistischen Psychopathen” im Kindesalter. *Archiv für Psychiatrie und Nervenkrankheit.* 117, 76–136.
- Aston-Jones G, Cohen JD. 2005. An integrative theory of locus coeruleus-norepinephrine function: Adaptive Gain and Optimal Performance. *Annu Rev Neurosci.* 28:403–450.
- Aston-Jones G, Rajkowski J, Kubiak P. 1997. Conditioned responses of monkey locus coeruleus neurons anticipate acquisition of discriminative behavior in a vigilance task. *Neuroscience.* 80:697–715.
- Auksztulewicz R, Spitzer B, Goltz D, Blankenburg F. 2011. Impairing somatosensory working memory using rTMS. *Eur J Neurosci.* 34:839–844.
- Autism Genome Project Consortium, Szatmari P, Paterson AD, Zwaigenbaum L, Roberts W, Brian J, ..., Meyer KJ. 2007. Mapping autism risk loci using genetic linkage and chromosomal rearrangements. *Nat Genet.* 39:319–328.
- Bailey A, Luthert P, Dean A, Harding B, Janota I, Montgomery M, Rutter M, Lantos P. 1998. A clinicopathological study of autism. *Brain.* 121:889–905.
- Balsters JH, Apps MAJ, Bolis D, Lehner R, Gallagher L, Wenderoth N. 2017. Disrupted prediction errors index social deficits in autism spectrum disorder. *Brain J Neurol.* 140:235–246.
- Bar M. 2004. Visual objects in context. *Nat Rev Neurosci.* 5:617–629.
- Bar M. 2007. The proactive brain: using analogies and associations to generate predictions. *Trends Cogn Sci.* 11:280–289.
- Bar M. 2009. The proactive brain: memory for predictions. *Philos Trans R Soc Lond B Biol Sci.* 364:1235–1243.
- Bar M, Aminoff E. 2003. Cortical analysis of visual context. *Neuron.* 38:347–358.
- Bar M, Kassam KS, Ghuman AS, Boshyan J, Schmid AM, Dale AM, Hamalainen MS, Marinkovic K, Schacter DL, Rosen BR, Halgren E. 2006. Top-down facilitation of visual recognition. *Proc Natl Acad Sci.* 103:449–454.
- Barcelo F, Knight RT. 2007. An information-theoretical approach to contextual processing in the human brain: evidence from prefrontal lesions. *Cereb Cortex N Y N 1991.* 17 Suppl 1:i51-60.
- Barlow H, Tripathy SP. 1997. Correspondence noise and signal pooling in the detection of coherent visual motion. *J Neurosci Off J Soc Neurosci.* 17:7954–7966.
- Baron-Cohen S. 2009. Autism: the empathizing-systemizing (E-S) theory. *Ann N Y Acad Sci.* 1156:68–80.
- Baron-Cohen S, Ashwin E, Ashwin C, Tavassoli T, Chakrabarti B. 2009. Talent in autism: hyper-systemizing, hyper-attention to detail and sensory hypersensitivity. *Philos Trans R Soc Lond B Biol Sci.* 364:1377–1383.
- Baron-Cohen S, Leslie AM, Frith U. 1985. Does the autistic child have a “theory of mind”? *Cognition.* 21:37–46.
- Baron-Cohen S, Ring HA, Bullmore ET, Wheelwright S, Ashwin C, Williams SC. 2000. The amygdala theory of autism. *Neurosci Biobehav Rev.* 24:355–364.
- Baron-Cohen S, Ring HA, Wheelwright S, Bullmore ET, Brammer MJ, Simmons A, Williams SC. 1999. Social intelligence in the normal and autistic brain: an fMRI study. *Eur J Neurosci.* 11:1891–1898.

- Baron-Cohen S, Wheelwright S, Skinner R, Martin J, Clubley E. 2001. The autism-spectrum quotient (AQ): evidence from Asperger syndrome/high-functioning autism, males and females, scientists and mathematicians. *J Autism Dev Disord.* 31:5–17.
- Barredo J, Verstynen TD, Badre D. 2016. Organization of cortico-cortical pathways supporting memory retrieval across subregions of the left ventrolateral prefrontal cortex. *J Neurophysiol.* 116:920–937.
- Bartlett, F. C. 1932. *Remembering: A study in experimental and social psychology.* Camb Engl Camb Univ Press.
- Bastin J, Deman P, David O, Gueguen M, Benis D, Minotti L, Hoffman D, Combrisson E, Kujala J, Perrone-Bertolotti M, Kahane P, Lachaux J-P, Jerbi K. 2017. Direct Recordings from Human Anterior Insula Reveal its Leading Role within the Error-Monitoring Network. *Cereb Cortex N Y N 1991.* 27:1545–1557.
- Bastos AM, Urey WM, Adams RA, Mangun GR, Fries P, Friston KJ. 2012. Canonical microcircuits for predictive coding. *Neuron.* 76:695–711.
- Baum SH, Stevenson RA, Wallace MT. 2015. Behavioral, perceptual, and neural alterations in sensory and multisensory function in autism spectrum disorder. *Prog Neurobiol.* 134:140–160.
- Becchio C, Mari M, Castiello U. 2010. Perception of shadows in children with autism spectrum disorders. *PLoS One.* 5:e10582.
- Behrens TEJ, Woolrich MW, Walton ME, Rushworth MFS. 2007. Learning the value of information in an uncertain world. *Nat Neurosci.* 10:1214–1221.
- Bell AH, Summerfield C, Morin EL, Malecek NJ, Ungerleider LG. 2016. Encoding of Stimulus Probability in Macaque Inferior Temporal Cortex. *Curr Biol CB.* 26:2280–2290.
- Ben-Ari Y, Khalilov I, Kahle KT, Cherubini E. 2012. The GABA excitatory/inhibitory shift in brain maturation and neurological disorders. *Neurosci Rev J Bringing Neurobiol Neurol Psychiatry.* 18:467–486.
- Berns GS, Cohen JD, Mintun MA. 1997. Brain regions responsive to novelty in the absence of awareness. *Science.* 276:1272–1275.
- Bertone A, Mottron L, Jelenic P, Faubert J. 2005. Enhanced and diminished visuo-spatial information processing in autism depends on stimulus complexity. *Brain J Neurol.* 128:2430–2441.
- Best C, Arora S, Porter F, Doherty M. 2015. The Relationship Between Subthreshold Autistic Traits, Ambiguous Figure Perception and Divergent Thinking. *J Autism Dev Disord.* 45:4064–4073.
- Bittigau P, Ikonomidou C. 1997. Glutamate in neurologic diseases. *J Child Neurol.* 12:471–485.
- Brisson J, Warreyn P, Serres J, Foussier S, Adrien-Louis J. 2012. Motor anticipation failure in infants with autism: a retrospective analysis of feeding situations. *Autism Int J Res Pract.* 16:420–429.
- Brix MK, Ersland L, Hugdahl K, Grüner R, Posserud M-B, Hammar Å, Craven AR, Noeske R, Evans CJ, Walker HB, Midtvedt T, Beyer MK. 2015. Brain MR spectroscopy in autism spectrum disorder-the GABA excitatory/inhibitory imbalance theory revisited. *Front Hum Neurosci.* 9:365.
- Brock J. 2012. Alternative Bayesian accounts of autistic perception: comment on Pellicano and Burr. *Trends Cogn Sci.* 16:573–574.
- Brugger P, Brugger S. 1993. The easter bunny in october: is it disguised as a duck? *Percept Mot Skills.* 76:577–578.
- Buiter HJ, Windhorst AD, Huisman MC, Yaqub M, Knol DL, Fisher A, Lammertsma AA, Leysen JE. 2013. [11C]AF150(S), an agonist PET ligand for M1 muscarinic acetylcholine receptors. *EJNMMI Res.* 3:19.
- Bulf H, Johnson SP, Valenza E. 2011. Visual statistical learning in the newborn infant. *Cognition.* 121:127–132.
- Burd L, Kerbeshian J, Fisher W. 1985. Inquiry into the incidence of hyperlexia in a statewide population of children with pervasive developmental disorder. *Psychol Rep.* 57:236–238.
- Bylund DB, Chacko DM. 1999. Characterization of alpha2 adrenergic receptor subtypes in human ocular tissue homogenates. *Invest Ophthalmol Vis Sci.* 40:2299–2306.
- Carlsson LH, Norrelgen F, Kjellmer L, Westerlund J, Gillberg C, Fernell E. 2013. Coexisting disorders and problems in preschool children with autism spectrum disorders. *ScientificWorldJournal.* 2013:213979.
- Caron M-J, Mottron L, Berthiaume C, Dawson M. 2006. Cognitive mechanisms, specificity and neural underpinnings of visuospatial peaks in autism. *Brain.* 129:1789–1802.
- Carpenter AC, Schacter DL. 2016. Flexible retrieval: When true inferences produce false memories. *J Exp Psychol Learn Mem Cogn.*
- Carter CJ, Blizard RA. 2016. Autism genes are selectively targeted by environmental pollutants including pesticides, heavy metals, bisphenol A, phthalates and many others in food, cosmetics or household products. *Neurochem Int.*
- Casanova MF, Buxhoeveden DP, Switala AE, Roy E. 2002. Minicolumnar pathology in autism. *Neurology.* 58:428–432.
- Cattaneo L, Fabbri-Destro M, Boria S, Pieraccini C, Monti A, Cossu G, Rizzolatti G. 2007. Impairment of actions chains in autism and its possible role in intention understanding. *Proc Natl Acad Sci U S A.* 104:17825–17830.

- Chapman JB, Cutler MG. 1989. Effects of sodium valproate on development and social behaviour in the Mongolian gerbil. *Neurotoxicol Teratol.* 11:193–198.
- Chennu S, Noreika V, Gueorguiev D, Blenkmann A, Kochen S, Ibáñez A, Owen AM, Bekinschtein TA. 2013. Expectation and attention in hierarchical auditory prediction. *J Neurosci Off J Soc Neurosci.* 33:11194–11205.
- Chevallier C, Kohls G, Troiani V, Brodtkin ES, Schultz RT. 2012. The social motivation theory of autism. *Trends Cogn Sci.* 16:231–239.
- Choueiri RN, Zimmerman AW. 2017. New Assessments and Treatments in ASD. *Curr Treat Options Neurol.* 19:6.
- Christensen DL, Baio J, Van Naarden Braun K, Bilder D, Charles J, Constantino JN, Daniels J, Durkin MS, Fitzgerald RT, Kurzius-Spencer M, Lee L-C, Pettygrove S, Robinson C, Schulz E, Wells C, Wingate MS, Zahorodny W, Yeargin-Allsopp M, Centers for Disease Control and Prevention (CDC). 2016. Prevalence and Characteristics of Autism Spectrum Disorder Among Children Aged 8 Years--Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2012. *Morb Mortal Wkly Rep Surveill Summ Wash DC* 2002. 65:1–23.
- Christensen DL, Bilder DA, Zahorodny W, Pettygrove S, Durkin MS, Fitzgerald RT, Rice C, Kurzius-Spencer M, Baio J, Yeargin-Allsopp M. 2016. Prevalence and Characteristics of Autism Spectrum Disorder Among 4-Year-Old Children in the Autism and Developmental Disabilities Monitoring Network. *J Dev Behav Pediatr JDBP.* 37:1–8.
- Church BA, Krauss MS, Lopata C, Toomey JA, Thomeer ML, Coutinho MV, Volker MA, Mercado E. 2010. Atypical Categorization in Children with High Functioning Autism Spectrum Disorder. *Psychon Bull Rev.* 17:862–868.
- Cicchini GM, Arrighi R, Cecchetti L, Giusti M, Burr DC. 2012. Optimal encoding of interval timing in expert percussionists. *J Neurosci Off J Soc Neurosci.* 32:1056–1060.
- Ciesielski KT, Harris RJ. 1997. Factors related to performance failure on executive tasks in autism. *Child Neuropsychol.* 3:1–12.
- Clark A. 2013. Whatever Next? Predictive Brains, Situated Agents, and the Future of Cognitive Science. *Behav Brain Sci.* 36:181–204.
- Cléry H, Andersson F, Fonlupt P, Gomot M. 2013. Brain correlates of automatic visual change detection. *NeuroImage.* 75:117–122.
- Cléry H, Bonnet-Brilhault F, Lenoir P, Barthelemy C, Bruneau N, Gomot M. 2013. Atypical visual change processing in children with autism: an electrophysiological study. *Psychophysiology.* 50:240–252.
- Cochin S, Barthelemy C, Roux S, Martineau J. 1999. Observation and execution of movement: similarities demonstrated by quantified electroencephalography *Eur J Neurosci.*
- Colloca L, Benedetti F. 2005. Placebos and painkillers: is mind as real as matter? *Nat Rev Neurosci.* 6:545–552.
- Corbett JE, Venuti P, Melcher D. 2016. Perceptual Averaging in Individuals with Autism Spectrum Disorder. *Front Psychol.* 7:1735.
- Corlett PR, Frith CD, Fletcher PC. 2009. From drugs to deprivation: a Bayesian framework for understanding models of psychosis. *Psychopharmacology (Berl).* 206:515–530.
- Corlett PR, Honey GD, Krystal JH, Fletcher PC. 2011. Glutamatergic Model Psychoses: Prediction Error, Learning, and Inference. *Neuropsychopharmacology.* 36:294–315.
- Cornelissen P, Richardson A, Mason A, Fowler S, Stein J. 1995. Contrast sensitivity and coherent motion detection measured at photopic luminance levels in dyslexics and controls. *Vision Res.* 35:1483–1494.
- Courchesne E. 2003. Evidence of Brain Overgrowth in the First Year of Life in Autism. *JAMA.* 290:337.
- Courchesne E, Allen G. 1997. Prediction and preparation, fundamental functions of the cerebellum. *Learn Mem Cold Spring Harb N.* 4:1–35.
- Courchesne E, Karns CM, Davis HR, Ziccardi R, Carper RA, Tigue ZD, Chisum HJ, Moses P, Pierce K, Lord C, Lincoln AJ, Pizzo S, Schreibman L, Haas RH, Akshoomoff NA, Courchesne RY. 2001. Unusual brain growth patterns in early life in patients with autistic disorder - An MRI study. *Neurology.* 57:245–254.
- Courchesne E, Pierce K. 2005. Why the frontal cortex in autism might be talking only to itself: local over-connectivity but long-distance disconnection. *Curr Opin Neurobiol.* 15:225–230.
- Courchesne E, Pierce K, Schumann CM, Redcay E, Buckwalter JA, Kennedy DP, Morgan J. 2007. Mapping early brain development in autism. *Neuron.* 56:399–413.
- d'Acremont M, Schultz W, Bossaerts P. 2013. The Human Brain Encodes Event Frequencies While Forming Subjective Beliefs. *J Neurosci Off J Soc Neurosci.* 33:10887.
- Dakin S, Frith U. 2005. Vagaries of visual perception in autism. *Neuron.* 48:497–507.
- Damasio AR, Maurer RG. 1978. A neurological model for childhood autism. *Arch Neurol.* 35:777–786.
- Davis G, Plaisted-Grant K. 2015. Low endogenous neural noise in autism. *Autism Int J Res Pract.* 19:351–362.
- Dawson G, Munson J, Webb SJ, Nalty T, Abbott R, Toth K. 2007. Rate of Head Growth Decelerates and Symptoms Worsen in the Second Year of Life in Autism. *Biol Psychiatry.* 61:458–464.

- Dawson M, Mottron L, Morton A. 2005. Learning in Autism. *Cognitive Psychology of Memory*. Vol. [2] of *Learning and Memory: A Comprehensive Reference*: [759-772].
- D’Cruz A-M, Ragozzino ME, Mosconi MW, Shrestha S, Cook EH, Sweeney JA. 2013. Reduced behavioral flexibility in autism spectrum disorders. *Neuropsychology*. 27:152–160.
- De Felice A, Greco A, Calamandrei G, Minghetti L. 2016. Prenatal exposure to the organophosphate insecticide chlorpyrifos enhances brain oxidative stress and prostaglandin E2 synthesis in a mouse model of idiopathic autism. *J Neuroinflammation*. 13:149.
- de Gardelle V, Mamassian P. 2015. Weighting mean and variability during confidence judgments. *PloS One*. 10:e0120870.
- de Gee JW, Knapen T, Donner TH. 2014. Decision-related pupil dilation reflects upcoming choice and individual bias. *Proc Natl Acad Sci U S A*. 111:E618-625.
- De Martino B, Fleming SM, Garrett N, Dolan RJ. 2013. Confidence in value-based choice. *Nat Neurosci*. 16:105–110.
- DeLorey TM, Sahbaie P, Hashemi E, Li W-W, Salehi A, Clark JD. 2011. Somatosensory and Sensorimotor Consequences Associated with the Heterozygous Disruption of the Autism Candidate Gene, *Gabrb3*. *Behav Brain Res*. 216:36–45.
- Delorme R, Ey E, Toro R, Leboyer M, Gillberg C, Bourgeron T. 2013. Progress toward treatments for synaptic defects in autism. *Nat Med*. 19:685–694.
- Dementieva YA, Vance DD, Donnelly SL, Elston LA, Wolpert CM, Ravan SA, DeLong GR, Abramson RK, Wright HH, Cuccaro ML. 2005. Accelerated head growth in early development of individuals with autism. *Pediatr Neurol*. 32:102–108.
- den Ouden HEM, Daunizeau J, Roiser J, Friston KJ, Stephan KE. 2010. Striatal prediction error modulates cortical coupling. *J Neurosci Off J Soc Neurosci*. 30:3210–3219.
- DePape A-MR, Hall GBC, Tillmann B, Trainor LJ. 2012. Auditory processing in high-functioning adolescents with Autism Spectrum Disorder. *PloS One*. 7:e44084.
- Devitt AL, Schacter DL. 2016. False memories with age: Neural and cognitive underpinnings. *Neuropsychologia*. 91:346–359.
- Di Martino A, Yan C-G, Li Q, Denio E, Castellanos FX, Alaerts K, Anderson JS, Assaf M, Bookheimer SY, Dapretto M, Deen B, Delmonte S, Dinstein I, Ertl-Wagner B, Fair DA, Gallagher L, Kennedy DP, Keown CL, Keysers C, Lainhart JE, Lord C, Luna B, Menon V, Minshew NJ, Monk CS, Mueller S, Müller R-A, Nebel MB, Nigg JT, O’Hearn K, Pelphrey KA, Peltier SJ, Rudie JD, Sunaert S, Thioux M, Tyszka JM, Uddin LQ, Verhoeven JS, Wenderoth N, Wiggins JL, Mostofsky SH, Milham MP. 2014. The autism brain imaging data exchange: towards a large-scale evaluation of the intrinsic brain architecture in autism. *Mol Psychiatry*. 19:659–667.
- di Pellegrino G, Fadiga L, Fogassi L, Gallese V, Rizzolatti G. 1992. Understanding motor events: a neurophysiological study. *Exp Brain Res*. 91:176–180.
- Di Russo F, Lucci G, Sulpizio V, Berchicci M, Spinelli D, Pitzalis S, Galati G. 2016. Spatiotemporal brain mapping during preparation, perception, and action. *NeuroImage*. 126:1–14.
- Dichter GS. 2012. Functional magnetic resonance imaging of autism spectrum disorders. *Dialogues Clin Neurosci*. 14:319–351.
- Dichter GS, Felder JN, Bodfish JW. 2009. Autism is characterized by dorsal anterior cingulate hyperactivation during social target detection. *Soc Cogn Affect Neurosci*. 4:215–226.
- Dietert RR, Dietert JM, Dewitt JC. 2011. Environmental risk factors for autism. *Emerg Health Threats J*. 4.
- Ding Y-S, Lin K-S, Logan J. 2006. PET imaging of norepinephrine transporters. *Curr Pharm Des*. 12:3831–3845.
- Doeller CF, Opitz B, Mecklinger A, Krick C, Reith W, Schröger E. 2003. Prefrontal cortex involvement in preattentive auditory deviance detection: neuroimaging and electrophysiological evidence. *NeuroImage*. 20:1270–1282.
- Doyle-Thomas KAR, Card D, Soorya LV, Ting Wang A, Fan J, Anagnostou E. 2014. Metabolic mapping of deep brain structures and associations with symptomatology in autism spectrum disorders. *Res Autism Spectr Disord*. 8:44–51.
- Dreher J-C, Grafman J. 2002. The roles of the cerebellum and basal ganglia in timing and error prediction: Cerebellar and striatal functions in timing and error prediction. *Eur J Neurosci*. 16:1609–1619.
- Du L, Shan L, Wang B, Li H, Xu Z, Staal WG, Jia F. 2015. A Pilot Study on the Combination of Applied Behavior Analysis and Bumetanide Treatment for Children with Autism. *J Child Adolesc Psychopharmacol*. 25:585–588.
- Durand CM, Betancur C, Boeckers TM, Bockmann J, Chaste P, Fauchereau F, Nygren G, Rastam M, Gillberg IC, Anckarsäter H, Sponheim E, Goubran-Botros H, Delorme R, Chabane N, Mouren-Simeoni M-C, de Mas P, Bieth E, Rogé B, Héron D, Burglen L, Gillberg C, Leboyer M, Bourgeron T. 2007. Mutations in

- the gene encoding the synaptic scaffolding protein SHANK3 are associated with autism spectrum disorders. *Nat Genet.* 39:25–27.
- Duzel E, Guitart-Masip M. 2013. Not so uncertain at last: locus coeruleus and decision making. *Neuron.* 79:9–11.
- Eapen V, Cavanna AE, Robertson MM. 2016. Comorbidities, Social Impact, and Quality of Life in Tourette Syndrome. *Front Psychiatry.* 7.
- Edden RAE, Puts NAJ, Harris AD, Barker PB, Evans CJ. 2014. Gannet: A batch-processing tool for the quantitative analysis of gamma-aminobutyric acid–edited MR spectroscopy spectra. *J Magn Reson Imaging JMRI.* 40:1445–1452.
- Ego C, Bonhomme L, Orban de Xivry J-J, Da Fonseca D, Lefèvre P, Masson GS, Deruelle C. 2016. Behavioral characterization of prediction and internal models in adolescents with autistic spectrum disorders. *Neuropsychologia.* 91:335–345.
- Englund MP, Hellström Å. 2012. Presentation-order effects for aesthetic stimulus preference. *Atten Percept Psychophys.* 74:1499–1511.
- Eshel N, Tian J, Bukwich M, Uchida N. 2016. Dopamine neurons share common response function for reward prediction error. *Nat Neurosci.* 19:479–486.
- Fatemi SH, Aldinger KA, Ashwood P, Bauman ML, Blaha CD, Blatt GJ, Chauhan A, Chauhan V, Dager SR, Dickson PE, Estes AM, Goldowitz D, Heck DH, Kemper TL, King BH, Martin LA, Millen KJ, Mittleman G, Mosconi MW, Persico AM, Sweeney JA, Webb SJ, Welsh JP. 2012. Consensus paper: pathological role of the cerebellum in autism. *Cerebellum Lond Engl.* 11:777–807.
- Fatemi SH, Halt AR, Stary JM, Kanodia R, Schulz SC, Realmuto GR. 2002. Glutamic acid decarboxylase 65 and 67 kDa proteins are reduced in autistic parietal and cerebellar cortices. *Biol Psychiatry.* 52:805–810.
- Feldman H, Friston K. 2010. Attention, uncertainty, and free-energy. *Front Hum Neurosci.* 4:215.
- Ferri R, Elia M, Agarwal N, Lanuzza B, Musumeci SA, Pennisi G. 2003. The mismatch negativity and the P3a components of the auditory event-related potentials in autistic low-functioning subjects. *Clin Neurophysiol Off J Int Fed Clin Neurophysiol.* 114:1671–1680.
- Fiorillo CD, Tobler PN, Schultz W. 2003. Discrete coding of reward probability and uncertainty by dopamine neurons. *Science.* 299:1898–1902.
- Fletcher PC, Frith CD. 2009. Perceiving is believing: a Bayesian approach to explaining the positive symptoms of schizophrenia. *Nat Rev Neurosci.* 10:48–58.
- Folstein S, Rutter M. 1977. Genetic influences and infantile autism. *Nature.* 265:726–728.
- Fombonne E. 2003a. The prevalence of autism. *JAMA.* 289:87–89.
- Fombonne E. 2003b. Epidemiological surveys of autism and other pervasive developmental disorders: an update. *J Autism Dev Disord.* 33:365–382.
- Ford TC, Crewther DP. 2016. A Comprehensive Review of the (1)H-MRS Metabolite Spectrum in Autism Spectrum Disorder. *Front Mol Neurosci.* 9:14.
- Fournier KA, Hass CJ, Naik SK, Lodha N, Cauraugh JH. 2010. Motor Coordination in Autism Spectrum Disorders: A Synthesis and Meta-Analysis. *J Autism Dev Disord.* 40:1227–1240.
- Fournier KA, Kimberg CI, Radonovich KJ, Tillman MD, Chow JW, Lewis MH, Bodfish JW, Hass CJ. 2010. Decreased static and dynamic postural control in children with autism spectrum disorders. *Gait Posture.* 32:6–9.
- Franklin TB, Russig H, Weiss IC, Gräff J, Linder N, Michalon A, Vizi S, Mansuy IM. 2010. Epigenetic transmission of the impact of early stress across generations. *Biol Psychiatry.* 68:408–415.
- Friston K. 2002. Functional integration and inference in the brain. *Prog Neurobiol.* 68:113–143.
- Friston K. 2003. Learning and inference in the brain. *Neural Netw Off J Int Neural Netw Soc.* 16:1325–1352.
- Friston K, Harrison L, Penny W. 2003. Dynamic causal modelling. *NeuroImage.* 19:1273–1302.
- Friston K. 2005. A theory of cortical responses. *Philos Trans R Soc Lond B Biol Sci.* 360:815–836.
- Friston K, Kilner J, Harrison L. 2006. A free energy principle for the brain. *J Physiol Paris.* 100:70–87.
- Friston K. 2008. Hierarchical models in the brain. *PLoS Comput Biol.* 4:e1000211.
- Friston K. 2010. The free-energy principle: a unified brain theory? *Nat Rev Neurosci.* 11:127–138.
- Friston K, Daunizeau J, Kilner J, Kiebel SJ. 2010. Action and behavior: a free-energy formulation. *Biol Cybern.* 102:227–260.
- Friston K, Mattout J, Kilner J. 2011. Action understanding and active inference. *Biol Cybern.* 104:137–160.
- Friston K. 2012a. Prediction, perception and agency. *Int J Psychophysiol, Predictive information processing in the brain: Principles, neural mechanisms and models.* 83:248–252.
- Friston K. 2012b. The history of the future of the Bayesian brain. *NeuroImage.* 62:1230–1233.
- Friston K, Lawson R, Frith CD. 2013. On hyperpriors and hypopriors: comment on Pellicano and Burr. *Trends Cogn Sci.* 17:1.
- Friston K. 2016. The Bayesian Savant. *ResearchGate.* 80:87–89.

- Frith U. 1989. *Autism: explaining the enigma*. Oxford UK ;;Cambridge MA USA: Basil Blackwell.
- Frith U. 1991. *Autism and Asperger Syndrome*. Cambridge University Press.
- Funahashi S. 2001. Neuronal mechanisms of executive control by the prefrontal cortex. *Neurosci Res*. 39:147–165.
- Gaetz W, Bloy L, Wang DJ, Port RG, Blaskey L, Levy SE, Roberts TPL. 2014. GABA estimation in the brains of children on the autism spectrum: measurement precision and regional cortical variation. *NeuroImage*. 86:1–9.
- Gallese V, Fadiga L, Fogassi L, Rizzolatti G. 1996. Action recognition in the premotor cortex. *Brain*. 119:593–609.
- Gallese V, Rochat MJ, Berchio C. 2013. The mirror mechanism and its potential role in autism spectrum disorder. *Dev Med Child Neurol*. 55:15–22.
- Gardener H, Spiegelman D, Buka SL. 2011. Perinatal and Neonatal Risk Factors for Autism: A Comprehensive Meta-analysis. *PEDIATRICS*. 128:344–355.
- Garrido MI, Kilner JM, Stephan KE, Friston KJ. 2009. The mismatch negativity: a review of underlying mechanisms. *Clin Neurophysiol Off J Int Fed Clin Neurophysiol*. 120:453–463.
- Gasparovic C, Neeb H, Feis DL, Damaraju E, Chen H, Doty MJ, South DM, Mullins PG, Bockholt HJ, Shah NJ. 2009. Quantitative spectroscopic imaging with in situ measurements of tissue water T1, T2, and density. *Magn Reson Med*. 62:583–590.
- Gastgeb HZ, Dundas EM, Minshew NJ, Strauss MS. 2012. Category formation in autism: can individuals with autism form categories and prototypes of dot patterns? *J Autism Dev Disord*. 42:1694–1704.
- Georgiades S, Szatmari P, Zwaigenbaum L, Bryson S, Brian J, Roberts W, Smith I, Vaillancourt T, Roncadin C, Garon N. 2013. A prospective study of autistic-like traits in unaffected siblings of probands with autism spectrum disorder. *JAMA Psychiatry*. 70:42–48.
- Gerardin P, Kourtzi Z, Mamassian P. 2010. Prior knowledge of illumination for 3D perception in the human brain. *Proc Natl Acad Sci*. 107:16309–16314.
- Giard MH, Perrin F, Pernier J, Bouchet P. 1990. Brain generators implicated in the processing of auditory stimulus deviance: a topographic event-related potential study. *Psychophysiology*. 27:627–640.
- Gillberg C, Fernell E. 2014. Autism plus versus autism pure. *J Autism Dev Disord*. 44:3274–3276.
- Glasson EJ, Bower C, Petterson B, de Klerk N, Chaney G, Hallmayer JF. 2004. Perinatal Factors and the Development of Autism: A Population Study. *Arch Gen Psychiatry*. 61:618.
- Gold PE. 2003. Acetylcholine modulation of neural systems involved in learning and memory. *Neurobiol Learn Mem*. 80:194–210.
- Gomot M, Belmonte MK, Bullmore ET, Bernard FA, Baron-Cohen S. 2008. Brain hyper-reactivity to auditory novel targets in children with high-functioning autism. *Brain*. 131:2479–2488.
- Gomot M, Bernard FA, Davis MH, Belmonte MK, Ashwin C, Bullmore ET, Baron-Cohen S. 2006. Change detection in children with autism: an auditory event-related fMRI study. *NeuroImage*. 29:475–484.
- Gomot M, Blanc R, Clery H, Roux S, Barthelemy C, Bruneau N. 2011. Candidate electrophysiological endophenotypes of hyper-reactivity to change in autism. *J Autism Dev Disord*. 41:705–714.
- Gomot M, Giard M-H, Adrien J-L, Barthelemy C, Bruneau N. 2002. Hypersensitivity to acoustic change in children with autism: electrophysiological evidence of left frontal cortex dysfunctioning. *Psychophysiology*. 39:577–584.
- Gomot M, Wicker B. 2012. A challenging, unpredictable world for people with autism spectrum disorder. *Int J Psychophysiol Off J Int Organ Psychophysiol*. 83:240–247.
- Gonzalez-Gadea ML, Chennu S, Bekinshtein TA, Rattazzi A, Beraudi A, Tripicchio P, Moyano B, Soffita Y, Steinberg L, Adolphi F, Sigman M, Marino J, Manes F, Ibanez A. 2015. Predictive coding in autism spectrum disorder and attention deficit hyperactivity disorder. *J Neurophysiol*. 114:2625–2636.
- Gotham K, Unruh K, Lord C. 2015. Depression and its measurement in verbal adolescents and adults with autism spectrum disorder. *Autism Int J Res Pract*. 19:491–504.
- Gowen E, Hamilton A. 2013. Motor abilities in autism: a review using a computational context. *J Autism Dev Disord*. 43:323–344.
- Grandin, T. 1997. A personal perspective on autism. In *Handbook of Autism and Pervasive Developmental Disorders* (Cohen, D.J. and Volkmar, F.R., eds). p. 1032–1042.
- Green D, Charman T, Pickles A, Chandler S, Loucas T, Simonoff E, Baird G. 2009. Impairment in movement skills of children with autistic spectrum disorders. *Dev Med Child Neurol*. 51:311–316.
- Gregory RL. 1968. Perceptual Illusions and Brain Models. *Proc R Soc Lond B Biol Sci*. 171:279–296.
- Gregory RL. 1980. Perceptions as hypotheses. *Philos Trans R Soc Lond B Biol Sci*. 290:181–197.
- Gustafsson L. 1997. Inadequate cortical feature maps: A neural circuit theory of autism. *Biol Psychiatry*. 42:1138–1147.
- Ha S, Sohn I-J, Kim N, Sim HJ, Cheon K-A. 2015. Characteristics of Brains in Autism Spectrum Disorder: Structure, Function and Connectivity across the Lifespan. *Exp Neurobiol*. 24:273–284.

- Hadjikhani N, Joseph RM, Snyder J, Tager-Flusberg H. 2006. Anatomical differences in the mirror neuron system and social cognition network in autism. *Cereb Cortex*. 16:1276–1282.
- Hadjikhani N, Zürcher NR, Rogier O, Ruest T, Hippolyte L, Ben-Ari Y, Lemonnier E. 2015. Improving emotional face perception in autism with diuretic bumetanide: a proof-of-concept behavioral and functional brain imaging pilot study. *Autism Int J Res Pract*. 19:149–157.
- Haker H, Schneebeli M, Stephan KE. 2016. Can Bayesian Theories of Autism Spectrum Disorder Help Improve Clinical Practice? *Front Psychiatry*. 7.
- Hallmayer J. 2011. Genetic Heritability and Shared Environmental Factors Among Twin Pairs With Autism. *Arch Gen Psychiatry*. 68:1095.
- Hamilton AF de C. 2013. Reflecting on the mirror neuron system in autism: a systematic review of current theories. *Dev Cogn Neurosci*. 3:91–105.
- Hansen SN, Schendel DE, Parner ET. 2015. Explaining the increase in the prevalence of autism spectrum disorders: the proportion attributable to changes in reporting practices. *JAMA Pediatr*. 169:56–62.
- Happé F, Frith U. 2006. The Weak Coherence Account: Detail-focused Cognitive Style in Autism Spectrum Disorders. *J Autism Dev Disord*. 36:5–25.
- Happé FG. 1996. Studying weak central coherence at low levels: children with autism do not succumb to visual illusions. A research note. *J Child Psychol Psychiatry*. 37:873–877.
- Harada M, Taki MM, Nose A, Kubo H, Mori K, Nishitani H, Matsuda T. 2011. Non-invasive evaluation of the GABAergic/glutamatergic system in autistic patients observed by MEGA-editing proton MR spectroscopy using a clinical 3 tesla instrument. *J Autism Dev Disord*. 41:447–454.
- Hari R, Forss N, Avikainen S, Kirveskari E, Salenius S, Rizzolatti G. 1998. Activation of human primary motor cortex during action observation: A neuromagnetic study. *Proc Natl Acad Sci*. 95:15061–15065.
- Harris AD, Puts NAJ, Edden RAE. 2015. Tissue correction for GABA-edited MRS: Considerations of voxel composition, tissue segmentation, and tissue relaxations. *J Magn Reson Imaging JMRI*. 42:1431–1440.
- Harris H, Israeli D, Minschew N, Bonneh Y, Heeger DJ, Behrmann M, Sagi D. 2015. Perceptual learning in autism: over-specificity and possible remedies. *Nat Neurosci*. 18:1574–1576.
- Harris JA, Arabzadeh E, Fairhall AL, Benito C, Diamond ME. 2006. Factors Affecting Frequency Discrimination of Vibrotactile Stimuli: Implications for Cortical Encoding. *PLoS ONE*. 1.
- Hasselmo ME. 2006. The role of acetylcholine in learning and memory. *Curr Opin Neurobiol*. 16:710–715.
- Hazlett HC, Poe M, Gerig G, Smith RG, Provenzale J, Ross A, Gilmore J, Piven J. 2005. Magnetic resonance imaging and head circumference study of brain size in autism: birth through age 2 years. *Arch Gen Psychiatry*. 62:1366–1376.
- Hellström Å, Rammsayer TH. 2015. Time-order errors and standard-position effects in duration discrimination: An experimental study and an analysis by the sensation-weighting model. *Atten Percept Psychophys*. 77:2409–2423.
- Herding J, Spitzer B, Blankenburg F. 2016. Upper Beta Band Oscillations in Human Premotor Cortex Encode Subjective Choices in a Vibrotactile Comparison Task. *J Cogn Neurosci*. 28:668–679.
- Herlihy L, Knoch K, Vibert B, Fein D. 2015. Parents' first concerns about toddlers with autism spectrum disorder: effect of sibling status. *Autism Int J Res Pract*. 19:20–28.
- Herry C, Bach DR, Esposito F, Di Salle F, Perrig WJ, Scheffler K, Lüthi A, Seifritz E. 2007. Processing of temporal unpredictability in human and animal amygdala. *J Neurosci Off J Soc Neurosci*. 27:5958–5966.
- Hill EL. 2004. Executive dysfunction in autism. *Trends Cogn Sci*. 8:26–32.
- Hillmer AT, Zheng M-Q, Li S, Scheunemann M, Lin S, Holden D, Labaree D, Ropchan J, Teodoro R, Deuther-Conrad W, Carson RE, Brust P, Huang Y. 2016. PET imaging evaluation of [(18)F]DBT-10, a novel radioligand specific to  $\alpha 7$  nicotinic acetylcholine receptors, in nonhuman primates. *Eur J Nucl Med Mol Imaging*. 43:537–547.
- Hollingworth HL. 1910. The Central Tendency of Judgment. *J Philos Psychol Sci Methods*. 7:461–469.
- Holder J, Lavender T, Mendez MA, O’Gorman R, Daly E, Craig MC, Lythgoe DJ, Barker GJ, Murphy DG. 2013. Reduced subcortical glutamate/glutamine in adults with autism spectrum disorders: a [<sup>1</sup>H]MRS study. *Transl Psychiatry*. 3:e279.
- Holder J, Wilson CE, Mendez MA, Murphy DG. 2014. Autistic traits and abnormal sensory experiences in adults. *J Autism Dev Disord*. 44:1461–1469.
- Horlin C, Black M, Falkmer M, Falkmer T. 2016. Proficiency of individuals with autism spectrum disorder at disembedding figures: A systematic review. *Dev Neurorehabilitation*. 19:54–63.
- Howlin P, Goode S, Hutton J, Rutter M. 2009. Savant skills in autism: psychometric approaches and parental reports. *Philos Trans R Soc B Biol Sci*. 364:1359–1367.
- Hudson M, Nicholson T, Ellis R, Bach P. 2016. I see what you say: Prior knowledge of other’s goals automatically biases the perception of their actions. *Cognition*. 146:245–250.



- Huettel SA. 2005. Decisions under Uncertainty: Probabilistic Context Influences Activation of Prefrontal and Parietal Cortices. *J Neurosci*. 25:3304–3311.
- Huguet G, Ey E, Bourgeron T. 2013. The genetic landscapes of autism spectrum disorders. *Annu Rev Genomics Hum Genet*. 14:191–213.
- Hyde KL, Samson F, Evans AC, Mottron L. 2010. Neuroanatomical Differences in Brain Areas Implicated in Perceptual and Other Core Features of Autism Revealed by Cortical Thickness Analysis and Voxel-Based Morphometry. *Hum Brain Mapp*. 31:556–566.
- Ide JS, Shenoy P, Yu AJ, Li CR. 2013. Bayesian prediction and evaluation in the anterior cingulate cortex. *J Neurosci Off J Soc Neurosci*. 33:2039–2047.
- Iglesias S, Mathys C, Brodersen KH, Kasper L, Piccirelli M, den Ouden HEM, Stephan KE. 2013. Hierarchical prediction errors in midbrain and basal forebrain during sensory learning. *Neuron*. 80:519–530.
- Ishikawa G, Ichihashi K. 2007. [Autistic psychopathy or pervasive developmental disorder: how has Asperger's syndrome changed in the past sixty years?]. *Nihon Rinsho Jpn J Clin Med*. 65:409–418.
- Ishizu T. 2013. Disambiguation of ambiguous figures in the brain. *Front Hum Neurosci*. 7:501.
- Ito H, Mori K, Harada M, Hisaoka S, Toda Y, Mori T, Goji A, Abe Y, Miyazaki M, Kagami S. 2017. A Proton Magnetic Resonance Spectroscopic Study in Autism Spectrum Disorder Using a 3-Tesla Clinical Magnetic Resonance Imaging (MRI) System: The Anterior Cingulate Cortex and the Left Cerebellum. *J Child Neurol*. 883073817702981.
- Jamain S, Quach H, Betancur C, Råstam M, Colineaux C, Gillberg IC, Soderstrom H, Giros B, Leboyer M, Gillberg C, [...], Van Maldergem L. 2003. Mutations of the X-linked genes encoding neuroligins NLGN3 and NLGN4 are associated with autism. *Nat Genet*. 34:27–29.
- James SJ, Shpyleva S, Melnyk S, Pavliv O, Pogribny IP. 2013. Complex epigenetic regulation of Engrailed-2 (EN-2) homeobox gene in the autism cerebellum. *Transl Psychiatry*. 3:e232.
- Jantzen KJ, Steinberg FL, Kelso JAS. 2004. Brain networks underlying human timing behavior are influenced by prior context. *Proc Natl Acad Sci U S A*. 101:6815–6820.
- Järvinen-Pasley A, Wallace GL, Ramus F, Happé F, Heaton P. 2008. Enhanced perceptual processing of speech in autism. *Dev Sci*. 11:109–121.
- Jazayeri M, Shadlen MN. 2010. Temporal context calibrates interval timing. *Nat Neurosci*. 13:1020–1026.
- Johansson RS, Cole KJ. 1992. Sensory-motor coordination during grasping and manipulative actions. *Curr Opin Neurobiol*. 2:815–823.
- Jones CRG, Happé F, Golden H, Marsden AJS, Tregay J, Simonoff E, Pickles A, Baird G, Charman T. 2009. Reading and arithmetic in adolescents with autism spectrum disorders: peaks and dips in attainment. *Neuropsychology*. 23:718–728.
- Just MA, Keller TA, Malave VL, Kana RK, Varma S. 2012. Autism as a neural systems disorder: a theory of frontal-posterior underconnectivity. *Neurosci Biobehav Rev*. 36:1292–1313.
- Kahneman D, Klein G. 2009. Conditions for intuitive expertise: a failure to disagree. *Am Psychol*. 64:515–526.
- Kaland N, Smith L, Mortensen EL. 2008. Brief Report: Cognitive Flexibility and Focused Attention in Children and Adolescents with Asperger Syndrome or High-Functioning Autism as Measured on the Computerized Version of the Wisconsin Card Sorting Test. *J Autism Dev Disord*. 38:1161–1165.
- Kaldy Z, Kraper C, Carter AS, Blaser E. 2011. Toddlers with Autism Spectrum Disorder are more successful at visual search than typically developing toddlers. *Dev Sci*. 14:980–988.
- Kana RK, Uddin LQ, Kenet T, Chugani D, MÅ¼aller R-A. 2014. Brain connectivity in autism. *Front Hum Neurosci*. 8.
- Kanner L. 1943. Autistic disturbances of affective contact. *Nervous Child*:2, 3, 217–250.
- Karaminis T, Cicchini GM, Neil L, Cappagli G, Aagten-Murphy D, Burr D, Pellicano E. 2016. Central tendency effects in time interval reproduction in autism. *Sci Rep*. 6:28570.
- Karim M, Harris JA, Langdon A, Breakspear M. 2013. The influence of prior experience and expected timing on vibrotactile discrimination. *Front Neurosci*. 7.
- Karvat G, Kimchi T. 2013. Acetylcholine Elevation Relieves Cognitive Rigidity and Social Deficiency in a Mouse Model of Autism. *Neuropsychopharmacol Off Publ Am Coll Neuropsychopharmacol*.
- Kemper TL, Bauman ML. 1993. The contribution of neuropathologic studies to the understanding of autism. *Neurol Clin*. 11:175–187.
- Kenworthy L, Yerys BE, Anthony LG, Wallace GL. 2008. Understanding Executive Control in Autism Spectrum Disorders in the Lab and in the Real World. *Neuropsychol Rev*. 18:320–338.
- Khan S, Michmizos K, Tommerdahl M, Ganesan S, Kitzbichler MG, Zetino M, Garel K-LA, Herbert MR, Hämäläinen MS, Kenet T. 2015. Somatosensory cortex functional connectivity abnormalities in autism show opposite trends, depending on direction and spatial scale. *Brain*. 138:1394.
- Kiebel SJ, Daunizeau J, Friston KJ. 2008. A hierarchy of time-scales and the brain. *PLoS Comput Biol*. 4:e1000209.

- Kikuchi M, Yoshimura Y, Shitamichi K, Ueno S, Hirose T, Munesue T, Ono Y, Tsubokawa T, Haruta Y, Oi M, Niida Y, Remijn GB, Takahashi T, Suzuki M, Higashida H, Minabe Y. 2013. A custom magnetoencephalography device reveals brain connectivity and high reading/decoding ability in children with autism. *Sci Rep.* 3:1139.
- Kilner JM, Friston KJ, Frith CD. 2007a. The mirror-neuron system: a Bayesian perspective. *Neuroreport.* 18:619–623.
- Kilner JM, Friston KJ, Frith CD. 2007b. Predictive coding: an account of the mirror neuron system. *Cogn Process.* 8:159–166.
- Kilner JM, Neal A, Weiskopf N, Friston KJ, Frith CD. 2009. Evidence of mirror neurons in human inferior frontal gyrus. *J Neurosci Off J Soc Neurosci.* 29:10153–10159.
- Kim H-G, Kishikawa S, Higgins AW, Seong I-S, Donovan DJ, Shen Y, Lally E, Weiss LA, Najm J, Kutsche K, Descartes M, Holt L, Braddock S, Troxell R, Kaplan L, Volkmar F, Klin A, Tsatsanis K, Harris DJ, Noens I, Pauls DL, Daly MJ, MacDonald ME, Morton CC, Quade BJ, Gusella JF. 2008. Disruption of Neurexin 1 Associated with Autism Spectrum Disorder. *Am J Hum Genet.* 82:199–207.
- Kim JE, Lyoo IK, Estes AM, Renshaw PF, Shaw DW, Friedman SD, Kim DJ, Yoon SJ, Hwang J, Dager SR. 2010. Laterobasal amygdalar enlargement in 6- to 7-year-old children with autism spectrum disorder. *Arch Gen Psychiatry.* 67:1187–1197.
- Kimura M. 2012. Visual mismatch negativity and unintentional temporal-context-based prediction in vision. *Int J Psychophysiol, Predictive information processing in the brain: Principles, neural mechanisms and models.* 83:144–155.
- King M, Bearman P. 2009. Diagnostic change and the increased prevalence of autism. *Int J Epidemiol.* 38:1224–1234.
- Kirkham NZ, Slemmer JA, Johnson SP. 2002. Visual statistical learning in infancy: evidence for a domain general learning mechanism. *Cognition.* 83:B35–42.
- Kitamura Y, Kozaka T, Miwa D, Uno I, Azim MA-U, Ogawa K, Taki J, Kinuya S, Shiba K. 2016. Synthesis and evaluation of a new vesamicol analog o-[(11)C]methyl-trans-decalinvesamicol as a PET ligand for the vesicular acetylcholine transporter. *Ann Nucl Med.* 30:122–129.
- Klinger LG, Dawson G. 2001. Prototype formation in autism. *Dev Psychopathol.* 13:111–124.
- Koldewyn K, Jiang YV, Weigelt S, Kanwisher N. 2013. Global/local processing in autism: not a disability, but a disinclination. *J Autism Dev Disord.* 43:2329–2340.
- Körding KP, Wolpert DM. 2004. Bayesian integration in sensorimotor learning. *Nature.* 427:244–247.
- Koster-Hale J, Saxe R. 2013. Theory of Mind: A Neural Prediction Problem. *Neuron.* 79:836–848.
- Kuhl BA, Bainbridge WA, Chun MM. 2012. Neural reactivation reveals mechanisms for updating memory. *J Neurosci Off J Soc Neurosci.* 32:3453–3461.
- Kujala T, Aho E, Lepistö T, Jansson-Verkasalo E, Nieminen-von Wendt T, von Wendt L, Näätänen R. 2007. Atypical pattern of discriminating sound features in adults with Asperger syndrome as reflected by the mismatch negativity. *Biol Psychol.* 75:109–114.
- Kveraga K, Ghuman AS, Bar M. 2007. Top-down predictions in the cognitive brain. *Brain Cogn.* 65:145–168.
- Lai M-C, Lombardo MV, Baron-Cohen S. 2014. Autism. *The Lancet.* 383:896–910.
- Lake CR, Ziegler MG, Murphy DL. 1977. Increased norepinephrine levels and decreased dopamine-beta-hydroxylase activity in primary autism. *Arch Gen Psychiatry.* 34:553–556.
- Lam KSL, Aman MG, Arnold LE. 2006. Neurochemical correlates of autistic disorder: a review of the literature. *Res Dev Disabil.* 27:254–289.
- Landrigan PJ. 2010. What causes autism? Exploring the environmental contribution. *Curr Opin Pediatr.* 22:219–225.
- Langham ME, Kitazawa Y, Hart RW. 1971. Adrenergic responses in the human eye. *J Pharmacol Exp Ther.* 179:47–55.
- Lawson RP, Friston KJ, Rees G. 2015. A more precise look at context in autism. *Proc Natl Acad Sci U S A.* 112:E5226.
- Lawson RP, Rees G, Friston KJ. 2014. An aberrant precision account of autism. *Front Hum Neurosci.* 8:302.
- Leblond CS, Heinrich J, Delorme R, Proepper C, Betancur C, Huguet G, ..., Bourgeron T. 2012. Genetic and functional analyses of SHANK2 mutations suggest a multiple hit model of autism spectrum disorders. *PLoS Genet.* 8:e1002521.
- Lecaignard F, Bertrand O, Gimenez G, Mattout J, Caclin A. 2015. Implicit learning of predictable sound sequences modulates human brain responses at different levels of the auditory hierarchy. *Front Hum Neurosci.* 9:505.
- Lee M, Martin-Ruiz C, Graham A, Court J, Jaros E, Perry R, Iversen P, Bauman M, Perry E. 2002. Nicotinic receptor abnormalities in the cerebellar cortex in autism. *Brain J Neurol.* 125:1483–1495.
- Leggio M, Molinari M. 2015. Cerebellar sequencing: a trick for predicting the future. *Cerebellum Lond Engl.* 14:35–38.

- Lemonnier E, Ben-Ari Y. 2010. The diuretic bumetanide decreases autistic behaviour in five infants treated during 3 months with no side effects. *Acta Paediatr Oslo Nor* 1992. 99:1885–1888.
- Lemonnier E, Villeneuve N, Sonie S, Serret S, Rosier A, Roue M, Brosset P, Viellard M, Bernoux D, Rondeau S, Thummler S, Ravel D, Ben-Ari Y. 2017. Effects of bumetanide on neurobehavioral function in children and adolescents with autism spectrum disorders. *Transl Psychiatry*. 7:e1056.
- Lewis JD, Theilmann RJ, Townsend J, Evans AC. 2013. Network efficiency in autism spectrum disorder and its relation to brain overgrowth. *Front Hum Neurosci*. 7:845.
- Leyfer OT, Folstein SE, Bacalman S, Davis NO, Dinh E, Morgan J, Tager-Flusberg H, Lainhart JE. 2006. Comorbid psychiatric disorders in children with autism: interview development and rates of disorders. *J Autism Dev Disord*. 36:849–861.
- Lieder F, Daunizeau J, Garrido MI, Friston KJ, Stephan KE. 2013. Modelling trial-by-trial changes in the mismatch negativity. *PLoS Comput Biol*. 9:e1002911.
- Lieder F, Stephan KE, Daunizeau J, Garrido MI, Friston KJ. 2013. A Neurocomputational Model of the Mismatch Negativity. *PLoS Comput Biol*. 9.
- Lim S-L, Cherry JBC, Davis AM, Balakrishnan SN, Ha O-R, Bruce JM, Bruce AS. 2016. The child brain computes and utilizes internalized maternal choices. *Nat Commun*. 7:11700.
- Linstead E, Dixon DR, French R, Granpeesheh D, Adams H, German R, Powell A, Stevens E, Tarbox J, Kornack J. 2017. Intensity and Learning Outcomes in the Treatment of Children With Autism Spectrum Disorder. *Behav Modif*. 41:229–252.
- Lortie M, Proulx-Bégin L, Saint-Amour D, Cousineau D, Théoret H, Lepage J-F. 2017. Brief Report: Biological Sound Processing in Children with Autistic Spectrum Disorder. *J Autism Dev Disord*.
- Lovaas OI. 1987. Behavioral treatment and normal educational and intellectual functioning in young autistic children. *J Consult Clin Psychol*. 55:3–9.
- Lugnegård T, Hallerbäck MU, Gillberg C. 2011. Psychiatric comorbidity in young adults with a clinical diagnosis of Asperger syndrome. *Res Dev Disabil*. 32:1910–1917.
- Ma WJ, Beck JM, Latham PE, Pouget A. 2006. Bayesian inference with probabilistic population codes. *Nat Neurosci*. 9:1432–1438.
- Magnuson KM, Constantino JN. 2011. Characterization of Depression in Children with Autism Spectrum Disorders. *J Dev Behav Pediatr JDBP*. 32:332–340.
- Mahajan R, Mostofsky SH. 2015. Neuroimaging endophenotypes in autism spectrum disorder. *CNS Spectr*. 20:412–426.
- Mandell DS, Morales KH, Xie M, Lawer LJ, Stahmer AC, Marcus SC. 2010. Age of diagnosis among Medicaid-enrolled children with autism, 2001-2004. *Psychiatr Serv Wash DC*. 61:822–829.
- Manning C, Dakin SC, Tibber MS, Pellicano E. 2014. Averaging, not internal noise, limits the development of coherent motion processing. *Dev Cogn Neurosci*. 10:44–56.
- Manning C, Kilner J, Neil L, Karaminis T, Pellicano E. 2016. Children on the autism spectrum update their behaviour in response to a volatile environment. *Dev Sci*.
- Manning C, Tibber MS, Charman T, Dakin SC, Pellicano E. 2015. Enhanced Integration of Motion Information in Children With Autism. *J Neurosci*. 35:6979.
- Markram H, Rinaldi T, Markram K. 2007. The intense world syndrome--an alternative hypothesis for autism. *Front Neurosci*. 1:77–96.
- Markram K, Markram H. 2010. The Intense World Theory – A Unifying Theory of the Neurobiology of Autism. *Front Hum Neurosci*. 4.
- Marrosu F, Marrosu G, Rachel MG, Biggio G. 1987. Paradoxical reactions elicited by diazepam in children with classic autism. *Funct Neurol*. 2:355–361.
- Martineau J, Cochin S, Magne R, Barthelemy C. 2008. Impaired cortical activation in autistic children: Is the mirror neuron system involved? *Int J Psychophysiol*. 68:35–40.
- Mathar D, Wilkinson L, Holl AK, Neumann J, Deserno L, Villringer A, Jahanshahi M, Horstmann A. 2016. The role of dopamine in positive and negative prediction error utilization during incidental learning - Insights from Positron Emission Tomography, Parkinson's disease and Huntington's disease. *Cortex J Devoted Study Nerv Syst Behav*.
- Mathys C, Daunizeau J, Friston KJ, Stephan KE. 2011. A bayesian foundation for individual learning under uncertainty. *Front Hum Neurosci*. 5:39.
- Mathys CD, Lomakina EI, Daunizeau J, Iglesias S, Brodersen KH, Friston KJ, Stephan KE. 2014. Uncertainty in perception and the Hierarchical Gaussian Filter. *Front Hum Neurosci*. 8.
- McBride PA, Anderson GM, Hertzog ME, Snow ME, Thompson SM, Khait VD, Shapiro T, Cohen DJ. 1998. Effects of diagnosis, race, and puberty on platelet serotonin levels in autism and mental retardation. *J Am Acad Child Adolesc Psychiatry*. 37:767–776.
- McCary LM, Roberts JE. 2013. Early identification of autism in fragile X syndrome: a review. *J Intellect Disabil Res JIDR*. 57:803–814.

- McPheeters ML, Weitlauf A, Vehorn A, Taylor C, Sathe NA, Krishnaswami S, Fonnesebeck C, Warren ZE. 2016. Screening for Autism Spectrum Disorder in Young Children: A Systematic Evidence Review for the U.S. Preventive Services Task Force, U.S. Preventive Services Task Force Evidence Syntheses, formerly Systematic Evidence Reviews. Rockville : Agency for Healthcare Research and Quality (US).
- Mescher M, Merkle H, Kirsch J, Garwood M, Gruetter R. 1998. Simultaneous in vivo spectral editing and water suppression. *NMR Biomed.* 11:266–272.
- Miller MB, Gazzaniga MS. 1998. Creating false memories for visual scenes. *Neuropsychologia.* 36:513–520.
- Miller SM. 1981. Predictability And Human Stress: Toward A Clarification Of Evidence And Theory. In: Berkowitz L, editor. *Advances in Experimental Social Psychology.* Academic Press. p. 203–256.
- Milne E. 2011. Increased Intra-Participant Variability in Children with Autistic Spectrum Disorders: Evidence from Single-Trial Analysis of Evoked EEG. *Front Psychol.* 2.
- Milne E, Swettenham J, Hansen P, Campbell R, Jeffries H, Plaisted K. 2002. High motion coherence thresholds in children with autism. *J Child Psychol Psychiatry.* 43:255–263.
- Minschew NJ, Sung K, Jones BL, Furman JM. 2004. Underdevelopment of the postural control system in autism. *Neurology.* 63:2056–2061.
- Mitchell P, Mottron L, Soulières I, Ropar D. 2010. Susceptibility to the Shepard illusion in participants with autism: reduced top-down influences within perception? *Autism Res Off J Int Soc Autism Res.* 3:113–119.
- Molloy CA, Dietrich KN, Bhattacharya A. 2003. Postural stability in children with autism spectrum disorder. *J Autism Dev Disord.* 33:643–652.
- Montague PR, Dolan RJ, Friston KJ, Dayan P. 2012. Computational psychiatry. *Trends Cogn Sci.* 16:72–80.
- Moran JM, Young LL, Saxe R, Lee SM, O’Young D, Mavros PL, Gabrieli JD. 2011. Impaired theory of mind for moral judgment in high-functioning autism. *Proc Natl Acad Sci U S A.* 108:2688–2692.
- Moran RJ, Campo P, Symmonds M, Stephan KE, Dolan RJ, Friston KJ. 2013. Free energy, precision and learning: the role of cholinergic neuromodulation. *J Neurosci Off J Soc Neurosci.* 33:8227–8236.
- Moriguchi S, Kimura Y, Ichise M, Arakawa R, Takano H, Seki C, Ikoma Y, Takahata K, Nagashima T, Yamada M, Mimura M, Suhara T. 2016. PET quantification of the norepinephrine transporter in human brain with (S,S)-18F-FMeNER-D2. *J Nucl Med Off Publ Soc Nucl Med.*
- Morris AL, Harris CL. 2002. Sentence context, word recognition, and repetition blindness. *J Exp Psychol Learn Mem Cogn.* 28:962–982.
- Möttönen R, Farmer H, Watkins KE. 2016. Neural basis of understanding communicative actions: Changes associated with knowing the actor’s intention and the meanings of the actions. *Neuropsychologia.* 81:230–237.
- Mottron L, Belleville S, Ménard E. 1999. Local bias in autistic subjects as evidenced by graphic tasks: perceptual hierarchization or working memory deficit? *J Child Psychol Psychiatry.* 40:743–755.
- Mottron L, Belleville S, Rouleau GA, Collignon O. 2014. Linking neocortical, cognitive, and genetic variability in autism with alterations of brain plasticity: the Trigger-Threshold-Target model. *Neurosci Biobehav Rev.* 47:735–752.
- Mottron L, Bouvet L, Bonnel A, Samson F, Burack JA, Dawson M, Heaton P. 2013. Veridical mapping in the development of exceptional autistic abilities. *Neurosci Biobehav Rev.* 37:209–228.
- Mottron L, Burack J. 2001. Enhanced perceptual functioning in the development of autism. In: *The development of autism: Perspectives from theory and research.* Burack, Charman, Yirmiya, Zelazo. ed. p. 131–148.
- Mottron L, Dawson M, Soulières I. 2009. Enhanced perception in savant syndrome: patterns, structure and creativity. *Philos Trans R Soc Lond B Biol Sci.* 364:1385–1391.
- Mottron L, Dawson M, Soulières I, Hubert B, Burack J. 2006. Enhanced perceptual functioning in autism: an update, and eight principles of autistic perception. *J Autism Dev Disord.* 36:27–43.
- Nassar MR, Rumsey KM, Wilson RC, Parikh K, Heasley B, Gold JJ. 2012. Rational regulation of learning dynamics by pupil-linked arousal systems. *Nat Neurosci.* 15:1040–1046.
- Neil L, Olsson NC, Pellicano E. 2016. The Relationship Between Intolerance of Uncertainty, Sensory Sensitivities, and Anxiety in Autistic and Typically Developing Children. *J Autism Dev Disord.* 46:1962–1973.
- Neufeld J, Roy M, Zapf A, Sinke C, Emrich HM, Prox-Vagedes V, Dillo W, Zedler M. 2013. Is synesthesia more common in patients with Asperger syndrome? *Front Hum Neurosci.* 7:847.
- Oberman LM, Hubbard EM, McCleery JP, Altschuler EL, Ramachandran VS, Pineda JA. 2005. EEG evidence for mirror neuron dysfunction in autism spectrum disorders. *Brain Res Cogn Brain Res.* 24:190–198.
- Oberman LM, Ramachandran VS, Pineda JA. 2008. Modulation of mu suppression in children with autism spectrum disorders in response to familiar or unfamiliar stimuli: the mirror neuron hypothesis. *Neuropsychologia.* 46:1558–1565.

- Oh J, Chambwe N, Klein S, Gal J, Andrews S, Gleason G, Shaknovich R, Melnick A, Campagne F, Toth M. 2013. Differential gene body methylation and reduced expression of cell adhesion and neurotransmitter receptor genes in adverse maternal environment. *Transl Psychiatry*. 3:e218.
- Ondobaka S, de Lange FP, Wittmann M, Frith CD, Bekkering H. 2015. Interplay Between Conceptual Expectations and Movement Predictions Underlies Action Understanding. *Cereb Cortex N Y N 1991*. 25:2566–2573.
- O’Riordan M, Plaisted K. 2001. Enhanced discrimination in autism. *Q J Exp Psychol A*. 54:961–979.
- O’Riordan MA, Plaisted KC, Driver J, Baron-Cohen S. 2001. Superior visual search in autism. *J Exp Psychol Hum Percept Perform*. 27:719–730.
- Ornitz EM. 1974. The modulation of sensory input and motor output in autistic children. *J Autism Child Schizophr*. 4:197–215.
- Ozonoff S, Jensen J. 1999. Brief report: specific executive function profiles in three neurodevelopmental disorders. *J Autism Dev Disord*. 29:171–177.
- Ozonoff S, Miller JN. 1995. Teaching theory of mind: A new approach to social skills training for individuals with autism. *J Autism Dev Disord*. 25:415–433.
- Ozonoff S, Pennington BF, Rogers SJ. 1991. Executive function deficits in high-functioning autistic individuals: relationship to theory of mind. *J Child Psychol Psychiatry*. 32:1081–1105.
- Palmer E. 1975. The effects of contextual scenes on the identification of objects. *Mem Cognit*. 3:519–526.
- Palmer CJ, Lawson RP, Hohwy J. 2017. Bayesian Approaches to Autism: Towards Volatility, Action, and Behavior. *Psychol Bull*.
- Payzan-LeNestour E, Dunne S, Bossaerts P, O’Doherty JP. 2013. The neural representation of unexpected uncertainty during value-based decision making. *Neuron*. 79:191–201.
- Pazo-Alvarez P, Cadaveira F, Amenedo E. 2003. MMN in the visual modality: a review. *Biol Psychol*. 63:199–236.
- Pell PJ, Mareschal I, Calder AJ, von dem Hagen EAH, Clifford CWG, Baron-Cohen S, Ewbank MP. 2016. Intact priors for gaze direction in adults with high-functioning autism spectrum conditions. *Mol Autism*. 7:25.
- Pellicano E, Burr D. 2012. When the world becomes “too real”: a Bayesian explanation of autistic perception. *Trends Cogn Sci*. 16:504–510.
- Pennington BF, Ozonoff S. 1996. Executive functions and developmental psychopathology. *J Child Psychol Psychiatry*. 37:51–87.
- Perry EK, Lee MLW, Martin-Ruiz CM, Court JA, Volsen SG, Merrit J, Folly E, Iversen PE, Bauman ML, Perry RH, Wenk GL. 2001. Cholinergic Activity in Autism: Abnormalities in the Cerebral Cortex and Basal Forebrain. *Am J Psychiatry*. 158:1058–1066.
- Persico AM, D’Agruma L, Maiorano N, Totaro A, Militerni R, Bravaccio C, Wassink TH, Schneider C, Melmed R, Trillo S, [...], Keller F, Collaborative Linkage Study of Autism. 2001. Reelin gene alleles and haplotypes as a factor predisposing to autistic disorder. *Mol Psychiatry*. 6:150–159.
- Petersen AK, Ahmad A, Shafiq M, Brown-Kipphut B, Fong C-T, Anwar Iqbal M. 2013. Deletion 1q43 encompassing only CHRM3 in a patient with autistic disorder. *Eur J Med Genet*. 56:118–122.
- Peterson CC, Slaughter V, Peterson J, Premack D. 2013. Children with autism can track others’ beliefs in a competitive game. *Dev Sci*. 16:443–450.
- Petrovic P, Dietrich T, Fransson P, Andersson J, Carlsson K, Ingvar M. 2005. Placebo in emotional processing--induced expectations of anxiety relief activate a generalized modulatory network. *Neuron*. 46:957–969.
- Phillips HN, Blenkmann A, Hughes LE, Bekinschtein TA, Rowe JB. 2015. Hierarchical Organization of Frontotemporal Networks for the Prediction of Stimuli across Multiple Dimensions. *J Neurosci Off J Soc Neurosci*. 35:9255–9264.
- Picci G, Gotts SJ, Scherf KS. 2016. A theoretical rut: revisiting and critically evaluating the generalized under/over-connectivity hypothesis of autism. *Dev Sci*. 19:524–549.
- Pierce K, Conant D, Hazin R, Stoner R, Desmond J. 2011. Preference for Geometric Patterns Early in Life as a Risk Factor for Autism. *Arch Gen Psychiatry*. 68:101.
- Pierce K, Glatt SJ, Liptak GS, McIntyre LL. 2009. The power and promise of identifying autism early: insights from the search for clinical and biological markers. *Ann Clin Psychiatry Off J Am Acad Clin Psychiatr*. 21:132–147.
- Pierce K, Müller RA, Ambrose J, Allen G, Courchesne E. 2001. Face processing occurs outside the fusiform “face area” in autism: evidence from functional MRI. *Brain J Neurol*. 124:2059–2073.
- Pinto D, Delaby E, Merico D, Barbosa M, Merikangas A, Klei L, ..., Scherer SW. 2014. Convergence of Genes and Cellular Pathways Dysregulated in Autism Spectrum Disorders. *Am J Hum Genet*. 94:677–694.
- Pinto D, Pagnamenta AT, Klei L, Anney R, Merico D, Regan R, ..., Betancur C. 2010. Functional impact of global rare copy number variation in autism spectrum disorders. *Nature*. 466:368–372.

- Pinto L, Goard MJ, Estandian D, Xu M, Kwan AC, Lee S-H, Harrison TC, Feng G, Dan Y. 2013. Fast modulation of visual perception by basal forebrain cholinergic neurons. *Nat Neurosci.* 16:1857–1863.
- Plaisted K, O’Riordan M, Baron-Cohen S. 1998. Enhanced discrimination of novel, highly similar stimuli by adults with autism during a perceptual learning task. *J Child Psychol Psychiatry.* 39:765–775.
- Plaisted KC. 2001. Reduced generalization in autism: An alternative to weak central coherence. In: Burack JA,, Charman T,, Yirmiya N,, Zelazo PR, editors. *The development of autism: Perspectives from theory and research.* Mahwah, NJ, US: Lawrence Erlbaum Associates Publishers. p. 149–169.
- Polšek D, Jagatic T, Capanec M, Hof PR, Simić G. 2011. Recent developments in neuropathology of Autism Spectrum Disorders. *Transl Neurosci.* 2:256–264.
- Polyak A, Kubina RM, Girirajan S. 2015. Comorbidity of intellectual disability confounds ascertainment of autism: implications for genetic diagnosis. *Am J Med Genet B Neuropsychiatr Genet.* 168:600–608.
- Pouget A, Drugowitsch J, Kepecs A. 2016. Confidence and certainty: distinct probabilistic quantities for different goals. *Nat Neurosci.* 19:366.
- Poulton EC. 1989. *Bias in quantifying judgments.* Hove, East Sussex, UK Hillsdale, USA: L. Erlbaum Associates.
- Powell G, Meredith Z, McMillin R, Freeman TCA. 2016. Bayesian Models of Individual Differences: Combining Autistic Traits and Sensory Thresholds to Predict Motion Perception. *Psychol Sci.*
- Premack D, Woodruff G. 1978. Does the chimpanzee have a theory of mind? *Behav Brain Sci.* 1:515.
- Preuschhof C, Heekeren HR, Taskin B, Schubert T, Villringer A. 2006. Neural correlates of vibrotactile working memory in the human brain. *J Neurosci Off J Soc Neurosci.* 26:13231–13239.
- Preuschhof C, Schubert T, Villringer A, Heekeren HR. 2010. Prior Information biases stimulus representations during vibrotactile decision making. *J Cogn Neurosci.* 22:875–887.
- Preuschoff K, Bossaerts P. 2007. Adding prediction risk to the theory of reward learning. *Ann N Y Acad Sci.* 1104:135–146.
- Preuschoff K, ‘t Hart BM, Einhauser W. 2011. Pupil dilation signals surprise: evidence for noradrenaline’s role in decision making. *Decis Neurosci.* 5:115.
- Puts NAJ, Wodka EL, Harris AD, Crocetti D, Tommerdahl M, Mostofsky SH, Edden RAE. 2016. Reduced GABA and altered somatosensory function in children with autism spectrum disorder. *Autism Res Off J Int Soc Autism Res.*
- Qian N, Lipkin RM. 2011. A learning-style theory for understanding autistic behaviors. *Front Hum Neurosci.* 5:77.
- Quattrocki E, Friston K. 2014. Autism, oxytocin and interoception. *Neurosci Biobehav Rev.* 47C:410–430.
- Radulescu E, Minati L, Ganeshan B, Harrison NA, Gray MA, Beacher FDCC, Chatwin C, Young RCD, Critchley HD. 2013. Abnormalities in fronto-striatal connectivity within language networks relate to differences in grey-matter heterogeneity in Asperger syndrome. *NeuroImage Clin.* 2:716–726.
- Rao PN, Klinepeter K, Stewart W, Hayworth R, Grubs R, Pettenati MJ. 1994. Molecular cytogenetic analysis of a duplication Xp in a male: further delineation of a possible sex influencing region on the X chromosome. *Hum Genet.* 94:149–153.
- Rao RP, Ballard DH. 1999. Predictive coding in the visual cortex: a functional interpretation of some extra-classical receptive-field effects. *Nat Neurosci.* 2:79–87.
- Redcay E, Courchesne E. 2005. When is the brain enlarged in autism? A meta-analysis of all brain size reports. *Biol Psychiatry.* 58:1–9.
- Rinaldi T, Kulangara K, Antonello K, Markram H. 2007. Elevated NMDA receptor levels and enhanced postsynaptic long-term potentiation induced by prenatal exposure to valproic acid. *Proc Natl Acad Sci U S A.* 104:13501–13506.
- Rinaldi T, Silberberg G, Markram H. 2008. Hyperconnectivity of local neocortical microcircuitry induced by prenatal exposure to valproic acid. *Cereb Cortex N Y N 1991.* 18:763–770.
- Rinehart NJ, Bellgrove MA, Tonge BJ, Brereton AV, Howells-Rankin D, Bradshaw JL. 2006. An examination of movement kinematics in young people with high-functioning autism and Asperger’s disorder: further evidence for a motor planning deficit. *J Autism Dev Disord.* 36:757–767.
- Rinehart NJ, Bradshaw JL, Brereton AV, Tonge BJ. 2001. Movement preparation in high-functioning autism and Asperger disorder: a serial choice reaction time task involving motor reprogramming. *J Autism Dev Disord.* 31:79–88.
- Ritvo ER, Freeman BJ, Scheibel AB, Duong T, Robinson H, Guthrie D, Ritvo A. 1986. Lower Purkinje cell counts in the cerebella of four autistic subjects: initial findings of the UCLA-NSAC Autopsy Research Report. *Am J Psychiatry.* 143:862–866.
- Rizzolatti G, Craighero L. 2004. The mirror-neuron system. *Annu Rev Neurosci.* 27:169–192.
- Rizzolatti G, Fabbri-Destro M. 2010. Mirror neurons: from discovery to autism. *Exp Brain Res.* 200:223–237.
- Rizzolatti G, Fadiga L, Gallese V, Fogassi L. 1996. Premotor cortex and the recognition of motor actions. *Cogn Brain Res, Mental representations of motor acts.* 3:131–141.

- Roberts AC, Robbins TW, Weiskrantz L. 1998. *The Prefrontal Cortex Executive and Cognitive Functions*. Oxford University Press.
- Robertson AE, Simmons DR. 2013. The Relationship between Sensory Sensitivity and Autistic Traits in the General Population. *J Autism Dev Disord*. 43:775–784.
- Robertson CE, Kravitz DJ, Freyberg J, Baron-Cohen S, Baker CI. 2013. Slower Rate of Binocular Rivalry in Autism. *J Neurosci*. 33:16983–16991.
- Robertson CE, Ratai E-M, Kanwisher N. 2016. Reduced GABAergic Action in the Autistic Brain. *Curr Biol*. 26:80–85.
- Robic S, Sonié S, Fonlupt P, Henaff M-A, Touil N, Coricelli G, Mattout J, Schmitz C. 2014. Decision-Making in a Changing World: A Study in Autism Spectrum Disorders. *J Autism Dev Disord*.
- Rodgers J, Hodgson A, Shields K, Wright C, Honey E, Freeston M. 2016. Towards a Treatment for Intolerance of Uncertainty in Young People with Autism Spectrum Disorder: Development of the Coping with Uncertainty in Everyday Situations (CUES©) Programme. *J Autism Dev Disord*.
- Rogers SJ, Estes A, Lord C, Vismara L, Winter J, Fitzpatrick A, Guo M, Dawson G. 2012. Effects of a brief Early Start Denver model (ESDM)-based parent intervention on toddlers at risk for autism spectrum disorders: a randomized controlled trial. *J Am Acad Child Adolesc Psychiatry*. 51:1052–1065.
- Romo R, de Lafuente V. 2013. Conversion of sensory signals into perceptual decisions. *Prog Neurobiol*. 103:41–75.
- Romo R, Hernández A, Zainos A, Brody CD, Lemus L. 2000. Sensing without Touching: Psychophysical Performance Based on Cortical Microstimulation. *Neuron*. 26:273–278.
- Ropar D, Mitchell P. 2002. Shape constancy in autism: the role of prior knowledge and perspective cues. *J Child Psychol Psychiatry*. 43:647–653.
- Rosenberg A, Patterson JS, Angelaki DE. 2015. A computational perspective on autism. *Proc Natl Acad Sci U S A*. 112:9158–9165.
- Rossignol DA, Frye RE. 2014. The use of medications approved for Alzheimer’s disease in autism spectrum disorder: a systematic review. *Front Pediatr*. 2:87.
- Rossoni E, Feng J, Tirozzi B, Brown D, Leng G, Moos F. 2008. Emergent Synchronous Bursting of Oxytocin Neuronal Network. *PLOS Comput Biol*. 4:e1000123.
- Rubenstein JLR, Merzenich MM. 2003. Model of autism: increased ratio of excitation/inhibition in key neural systems. *Genes Brain Behav*. 2:255–267.
- Rumsey JM, Hamburger SD. 1990. Neuropsychological divergence of high-level autism and severe dyslexia. *J Autism Dev Disord*. 20:155–168.
- Russell J (Ed). 1997. *Autism as an executive disorder*. Oxford University Press.
- Sadacca BF, Jones JL, Schoenbaum G. 2016. Midbrain dopamine neurons compute inferred and cached value prediction errors in a common framework. *eLife*. 5.
- Saffran JR, Aslin RN, Newport EL. 1996. Statistical learning by 8-month-old infants. *Science*. 274:1926–1928.
- Samson F, Mottron L, Jemel B, Belin P, Ciocca V. 2005. Can Spectro-Temporal Complexity Explain the Autistic Pattern of Performance on Auditory Tasks? *J Autism Dev Disord*. 36:65–76.
- Samson F, Mottron L, Soulières I, Zeffiro TA. 2012. Enhanced visual functioning in autism: an ALE meta-analysis. *Hum Brain Mapp*. 33:1553–1581.
- Sanchez G. 2014 *Real-Time Electrophysiology in Cognitive Neuroscience: Towards Adaptive Paradigms to study perceptual Learning and Decision-Making in Humans*. PhD Thesis Claude Bernard Lyon 1 Univ.
- Schain RJ, Freedman DX. 1961. Studies on 5-hydroxyindole metabolism in autistic and other mentally retarded children. *J Pediatr*. 58:315–320.
- Schiffer A-M, Ahlheim C, Wurm MF, Schubotz RI. 2012. Surprised at All the Entropy: Hippocampal, Caudate and Midbrain Contributions to Learning from Prediction Errors. *PLOS ONE*. 7:e36445.
- Schiffer A-M, Schubotz RI. 2011. Caudate nucleus signals for breaches of expectation in a movement observation paradigm. *Front Hum Neurosci*. 5:38.
- Schlangen D, Barenholtz E. 2015. Intrinsic and contextual features in object recognition. *J Vis*. 15:15.1.28.
- Schmitz C, Assaiante C. 2008. Postural control in children with autism spectrum disorder. In: *Posture: a key issue in developmental disorders*. In: M. Hadders-Algra and E. Brogren Carlberg. Mac Keith Press, London. ed. p. 253–269.
- Schmitz C, Jenmalm P, Ehrsson HH, Forssberg H. 2005. Brain activity during predictable and unpredictable weight changes when lifting objects. *J Neurophysiol*. 93:1498–1509.
- Schmitz C, Martineau J, Barthélémy C, Assaiante C. 2003. Motor control and children with autism: deficit of anticipatory function? *Neurosci Lett*. 348:17–20.
- Schovanec J, Glorion C, Revil S, Ameisen JC. 2013. *Je suis à l’Est ! édition revue et corrigée*. ed. Pocket.
- Schrodt F, Layher G, Neumann H, Butz MV. 2015. Embodied learning of a generative neural model for biological motion perception and inference. *Front Comput Neurosci*. 9:79.

- Schultz W. 2016a. Dopamine reward prediction-error signalling: a two-component response. *Nat Rev Neurosci.* 17:183–195.
- Schultz W. 2016b. Dopamine reward prediction error coding. *Dialogues Clin Neurosci.* 18:23–32.
- Schultz W, Dickinson A. 2000. Neuronal coding of prediction errors. *Annu Rev Neurosci.* 23:473–500.
- Sealey LA, Hughes BW, Sriskanda AN, Guest JR, Gibson AD, Johnson-Williams L, Pace DG, Bagasra O. 2016. Environmental factors in the development of autism spectrum disorders. *Environ Int.* 88:288–298.
- Seriès P, Seitz AR. 2013. Learning what to expect (in visual perception). *Front Hum Neurosci.* 7:668.
- Sherman MT, Seth AK, Kanai R. 2016. Predictions Shape Confidence in Right Inferior Frontal Gyrus. *J Neurosci Off J Soc Neurosci.* 36:10323–10336.
- Shukla DK, Keehn B, Smylie DM, Müller R-A. 2011. Microstructural abnormalities of short-distance white matter tracts in autism spectrum disorder. *Neuropsychologia.* 49:1378–1382.
- Simmons D, Milne E. 2015. Response to Davis and Plaisted-Grant: Low or high endogenous neural noise in autism spectrum disorder? *Autism Int J Res Pract.* 19:363–364.
- Simmons DR, McKay L, McAleer P, Toal E, Robertson A, Pollick FE. 2007. Neural noise and autism spectrum disorders. *Perception.* 36:119–120.
- Simmons DR, Robertson AE, McKay LS, Toal E, McAleer P, Pollick FE. 2009. Vision in autism spectrum disorders. *Vision Res.* 49:2705–2739.
- Simms ML, Kemper TL, Timbie CM, Bauman ML, Blatt GJ. 2009. The anterior cingulate cortex in autism: heterogeneity of qualitative and quantitative cytoarchitectonic features suggests possible subgroups. *Acta Neuropathol (Berl).* 118:673–684.
- Simpson R, Devenyi GA, Jezzard P, Hennessy TJ, Near J. 2017. Advanced processing and simulation of MRS data using the FID appliance (FID-A)-An open source, MATLAB-based toolkit. *Magn Reson Med.* 77:23–33.
- Sinclair RJ, Burton H. 1996. Discrimination of vibrotactile frequencies in a delayed pair comparison task. *Percept Psychophys.* 58:680–692.
- Sinha P, Kjelgaard MM, Gandhi TK, Tsourides K, Cardinaux AL, Pantazis D, Diamond SP, Held RM. 2014. Autism as a disorder of prediction. *Proc Natl Acad Sci U S A.* 111:15220–15225.
- Smith AD, Kenny L, Rudnicka A, Briscoe J, Pellicano E. 2016. Drawing Firmer Conclusions: Autistic Children Show No Evidence of a Local Processing Bias in a Controlled Copying Task. *J Autism Dev Disord.* 46:3481–3492.
- Smith RS, Sharp J. 2013. Fascination and isolation: a grounded theory exploration of unusual sensory experiences in adults with Asperger syndrome. *J Autism Dev Disord.* 43:891–910.
- Sobel DM, Capps LM, Gopnik A. 2005. Ambiguous figure perception and theory of mind understanding in children with autistic spectrum disorders. *Br J Dev Psychol.* 23:159–174.
- Sokhadze EM, Casanova MF, Tasman A, Brockett S. 2016. Electrophysiological and Behavioral Outcomes of Berard Auditory Integration Training (AIT) in Children with Autism Spectrum Disorder. *Appl Psychophysiol Biofeedback.*
- Spitzer B, Wacker E, Blankenburg F. 2010. Oscillatory correlates of vibrotactile frequency processing in human working memory. *J Neurosci Off J Soc Neurosci.* 30:4496–4502.
- Steffenburg S, Gillberg C, Hellgren L, Andersson L, Gillberg IC, Jakobsson G, Bohman M. 1989. A twin study of autism in Denmark, Finland, Iceland, Norway and Sweden. *J Child Psychol Psychiatry.* 30:405–416.
- Steinberg EE, Keiflin R, Boivin JR, Witten IB, Deisseroth K, Janak PH. 2013. A causal link between prediction errors, dopamine neurons and learning. *Nat Neurosci.* 16:966–973.
- Stephan KE, Diaconescu AO, Iglesias S. 2016. Bayesian inference, dysconnectivity and neuromodulation in schizophrenia. *Brain J Neurol.* 139:1874–1876.
- Stephan KE, Mathys C. 2014. Computational approaches to psychiatry. *Curr Opin Neurobiol.* 25:85–92.
- Sterzer P, Frith C, Petrovic P. 2008. Believing is seeing: expectations alter visual awareness. *Curr Biol CB.* 18:R697–698.
- Summerfield C, Egner T, Greene M, Koechlin E, Mangels J, Hirsch J. 2006. Predictive Codes for Forthcoming Perception in the Frontal Cortex. *Science.* 314:1311–1314.
- Synofzik M, Lindner A, Thier P. 2008. The cerebellum updates predictions about the visual consequences of one's behavior. *Curr Biol CB.* 18:814–818.
- Takayama Y, Hashimoto R, Tani M, Kanai C, Yamada T, Watanabe H, Ono T, Kato N, Iwanami A. 2014. Standardization of the Japanese version of the Glasgow Sensory Questionnaire (GSQ). *Res Autism Spectr Disord.* 8:347–353.
- Tammet D. 2007. *Born on a Blue Day: Inside the Extraordinary Mind of an Autistic Savant: A Memoir.* Reprint. ed. New York: Free Press.
- Tassinari H, Hudson TE, Landy MS. 2006. Combining priors and noisy visual cues in a rapid pointing task. *J Neurosci Off J Soc Neurosci.* 26:10154–10163.



- Tebartz van Elst L, Maier S, Fangmeier T, Endres D, Mueller GT, Nickel K, Ebert D, Lange T, Hennig J, Biscaldi M, Riedel A, Perlov E. 2014. Disturbed cingulate glutamate metabolism in adults with high-functioning autism spectrum disorder: evidence in support of the excitatory/inhibitory imbalance hypothesis. *Mol Psychiatry*. 19:1314–1325.
- Tenenbaum JB, Kemp C, Griffiths TL, Goodman ND. 2011. How to grow a mind: statistics, structure, and abstraction. *Science*. 331:1279–1285.
- Thillay A, Lemaire M, Roux S, Houy-Durand E, Barthélémy C, Knight RT, Bidet-Caulet A, Bonnet-Brilhault F. 2016. Atypical Brain Mechanisms of Prediction According to Uncertainty in Autism. *Front Neurosci*. 10:317.
- Thomas NS, Sharp AJ, Browne CE, Skuse D, Hardie C, Dennis NR. 1999. Xp deletions associated with autism in three females. *Hum Genet*. 104:43–48.
- Thomas R, Nardini M, Mareschal D. 2010. Interactions between “light-from-above” and convexity priors in visual development. *J Vis*. 10:6.
- Tong J, Ngo V, Goldreich D. 2016. Tactile length contraction as Bayesian inference. *J Neurophysiol*. 116:369–379.
- Tordjman S, Somogyi E, Coulon N, Kermarrec S, Cohen D, Bronsard G, Bonnot O, Weismann-Arcache C, Botbol M, Lauth B, Ginchat V, Roubertoux P, Barburroth M, Kovess V, Geoffroy M-M, Xavier J. 2014. Gene × Environment Interactions in Autism Spectrum Disorders: Role of Epigenetic Mechanisms. *Front Psychiatry*. 5.
- Trapp S, Bar M. 2015. Prediction, context, and competition in visual recognition. *Ann N Y Acad Sci*. 1339:190–198.
- Uddin LQ, Supekar K, Menon V. 2013. Reconceptualizing functional brain connectivity in autism from a developmental perspective. *Front Hum Neurosci*. 7:458.
- Uppal N, Wicinski B, Buxbaum JD, Heinsen H, Schmitz C, Hof PR. 2014. Neuropathology of the anterior midcingulate cortex in young children with autism. *J Neuropathol Exp Neurol*. 73:891–902.
- van Boxtel JJA, Lu H. 2013. A predictive coding perspective on autism spectrum disorders. *Front Psychol*. 4.
- Van de Cruys S, de-Wit L, Evers K, Boets B, Wagemans J. 2013. Weak priors versus overfitting of predictions in autism: Reply to Pellicano and Burr (TICS, 2012). *Percept*. 4:95–97.
- Van de Cruys S, Evers K, Van der Hallen R, Van Eylen L, Boets B, de-Wit L, Wagemans J. 2014. Precise minds in uncertain worlds: predictive coding in autism. *Psychol Rev*. 121:649–675.
- Van de Cruys S, Van der Hallen R, Wagemans J. 2016. Disentangling signal and noise in autism spectrum disorder. *Brain Cogn*.
- Van der Hallen R, Evers K, Boets B, Steyaert J, Noens I, Wagemans J. 2016. Visual Search in ASD: Instructed Versus Spontaneous Local and Global Processing. *J Autism Dev Disord*. 46:3023–3036.
- Van der Hallen R, Evers K, Brewaeys K, Van den Noortgate W, Wagemans J. 2015. Global processing takes time: A meta-analysis on local-global visual processing in ASD. *Psychol Bull*. 141:549–573.
- Van Eylen L, Boets B, Cosemans N, Peeters H, Steyaert J, Wagemans J, Noens I. 2017. Executive functioning and local-global visual processing: candidate endophenotypes for autism spectrum disorder? *J Child Psychol Psychiatry*. 58:258–269.
- Vijayakumar NT, Judy MV. 2016. Autism spectrum disorders: Integration of the genome, transcriptome and the environment. *J Neurol Sci*. 364:167–176.
- Vilares I, Howard JD, Fernandes HL, Gottfried JA, Kording KP. 2012. Differential representations of prior and likelihood uncertainty in the human brain. *Curr Biol CB*. 22:1641–1648.
- Vladusich T, Olu-Lafe O, Kim D-S, Tager-Flusberg H, Grossberg S. 2010. Prototypical category learning in high-functioning autism. *Autism Res Off J Int Soc Autism Res*. 3:226–236.
- von der Lühe T, Manera V, Barisic I, Becchio C, Vogeley K, Schilbach L. 2016. Interpersonal predictive coding, not action perception, is impaired in autism. *Philos Trans R Soc Lond B Biol Sci*. 371.
- von Helmholtz. 1866. Helmholtz’s treatise on physiological optics. *J Appl Psychol*. 10:294–295.
- Wacongne C, Changeux J-P, Dehaene S. 2012. A Neuronal Model of Predictive Coding Accounting for the Mismatch Negativity. *J Neurosci*. 32:3665–3678.
- Weiss Y, Simoncelli EP, Adelson EH. 2002. Motion illusions as optimal percepts. *Nat Neurosci*. 5:598–604.
- Weitlauf AS, McPheeters ML, Peters B, Sathe N, Travis R, Aiello R, Williamson E, Veenstra-VanderWeele J, Krishnaswami S, Jerome R, Warren Z. 2014. Therapies for Children With Autism Spectrum Disorder: Behavioral Interventions Update, AHRQ Comparative Effectiveness Reviews. Rockville (MD): Agency for Healthcare Research and Quality (US).
- Wiener M, Thompson JC, Coslett HB. 2014. Continuous carryover of temporal context dissociates response bias from perceptual influence for duration. *PloS One*. 9:e100803.
- Williams JH, Whiten A, Suddendorf T, Perrett DI. 2001. Imitation, mirror neurons and autism. *Neurosci Biobehav Rev*. 25:287–295.

- Wilson M, Reynolds G, Kauppinen RA, Arvanitis TN, Peet AC. 2011. A constrained least-squares approach to the automated quantitation of in vivo  $^1\text{H}$  magnetic resonance spectroscopy data. *Magn Reson Med.* 65:1–12.
- Wing L. 1981. Asperger's syndrome: a clinical account. *Psychol Med.* 11:115–129.
- Wing L, Gould J. 1979. Severe impairments of social interaction and associated abnormalities in children: epidemiology and classification. *J Autism Dev Disord.* 9:11–29.
- Wong DF, Kuwabara H, Kim J, Brasic JR, Chamroomrat W, Gao Y, Valentine H, Willis W, Mathur A, McCaul ME, Wand G, Gean EG, Dannals RF, Horti AG. 2013. PET imaging of high-affinity  $\alpha 4\beta 2$  nicotinic acetylcholine receptors in humans with 18F-AZAN, a radioligand with optimal brain kinetics. *J Nucl Med Off Publ Soc Nucl Med.* 54:1308–1314.
- Xu F, Garcia V. 2008. Intuitive statistics by 8-month-old infants. *Proc Natl Acad Sci U S A.* 105:5012–5015.
- Yamada J, Okabe A, Toyoda H, Kilb W, Luhmann HJ, Fukuda A. 2004. Cl<sup>-</sup> uptake promoting depolarizing GABA actions in immature rat neocortical neurones is mediated by NKCC1. *J Physiol.* 557:829–841.
- Yang J, Hofmann J. 2016. Action observation and imitation in autism spectrum disorders: an ALE meta-analysis of fMRI studies. *Brain Imaging Behav.* 10:960–969.
- Yeargin-Allsopp M, Rice C, Karapurkar T, Doernberg N, Boyle C, Murphy C. 2003. Prevalence of Autism in a US Metropolitan Area. *JAMA.* 289.
- Yendiki A, Koldewyn K, Kakunoori S, Kanwisher N, Fischl B. 2014. Spurious group differences due to head motion in a diffusion MRI study. *NeuroImage.* 88:79.
- Yerys BE, Wallace GL, Sokoloff JL, Shook DA, James JD, Kenworthy L. 2009. Attention deficit/hyperactivity disorder symptoms moderate cognition and behavior in children with autism spectrum disorders. *Autism Res.* n/a-n/a.
- Yip J, Soghomonian J-J, Blatt GJ. 2007. Decreased GAD67 mRNA levels in cerebellar Purkinje cells in autism: pathophysiological implications. *Acta Neuropathol (Berl).* 113:559–568.
- Yu AJ, Dayan P. 2005. Uncertainty, neuromodulation, and attention. *Neuron.* 46:681–692.
- Zalla T, Labryère N, Clément A, Georgieff N. 2010. Predicting ensuing actions in children and adolescents with autism spectrum disorders. *Exp Brain Res.* 201:809–819.
- Zhang J. 2012. The Effects of Evidence Bounds on Decision-Making: Theoretical and Empirical Developments. *Front Psychol.* 3.
- Zielinski BA, Prigge MBD, Nielsen JA, Froehlich AL, Abildskov TJ, Anderson JS, Fletcher PT, Zygumnt KM, Travers BG, Lange N, Alexander AL, Bigler ED, Lainhart JE. 2014. Longitudinal changes in cortical thickness in autism and typical development. *Brain J Neurol.* 137:1799–1812.
- Zwaigenbaum L, Bauman ML, Stone WL, Yirmiya N, Estes A, Hansen RL, McPartland JC, Natowicz MR, Choueiri R, Fein D, Kasari C, Pierce K, Buie T, Carter A, Davis PA, Granpeesheh D, Mailloux Z, Newschaffer C, Robins D, Roley SS, Wagner S, Wetherby A. 2015. Early Identification of Autism Spectrum Disorder: Recommendations for Practice and Research. *Pediatrics.* 136 Suppl 1:S10-40.

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## SUPPLEMENTARY MATERIAL

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## Appendix 1: Pilot study of the time-order effect

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### Effect of priors on visual perceptual decisions

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#### **Abstract**

According to Bayesian brain theories of perception, our percepts are influenced both by the actual sensory input, and by *priors* learnt in our past experiences. Using a visual task, the present study aimed (1) at testing how priors induce a perceptual bias, (2) at assessing how increased sensory noise affect the perceptual bias, and (3) at studying whether the effect of sensory noise on perceptual bias is related to degrees of autistic traits.

Twenty-four adults were involved in a two-forced choice task where they watched two successively displayed grey discs and had to compare their luminance. This newly designed perceptual task was supposed to elicit a time-order effect (TOE), whereby the first stimulus is perceived as closer to the prior than it actually is. Here, the prior corresponded to the average luminance of the previously displayed stimuli. We tested three versions of this task: increased sensory noise in the first stimulus, or in the second stimulus, or no increased sensory noise.

The presentation of two discs of different luminance induced a TOE. Indeed, despite similar objective difficulty, the order of presentation could make the perceptual decision harder (58% of correct answers) or easier (95% of correct answers). The presentation of two discs of same luminance also induced a TOE: despite no luminance difference, the second disc was perceived as darker than the first one in 82% of the cases when discs were darker than the prior, whereas it was perceived as clearer than the first one in 87% of the cases when discs were clearer than the prior. The introduction of noise in the first or second stimulus did not significantly affect the perceptual bias, but its effect was negatively correlated with the autistic quotient.

In conclusion, this new visual task enables to assess the time-order effect with stimuli of different or same luminance. Yet, the introduction of noise might not have been sufficient to significantly induce a perceptual bias. Interestingly, adding sensory noise affected more individuals with fewer autistic traits. Further investigations should try to increase sensory noise even more, and to assess its effect in individuals with ASD.

## Material and Methods

### *Participants*

Twenty-four healthy adults took part in the experiment (seventeen females and seven males). The mean age was 25.6 years old ( $\pm 6.0$ ), and the mean education level was 3 years after baccalaureate ( $\pm 2.0$ ). Inclusion criteria were age (between 18 and 60 years) and being affiliated to the social security system. Every participant completed the Autism spectrum Quotient (AQ) questionnaire (Baron-Cohen et al. 2001), as well as the Glasgow Sensory Questionnaire (GSQ) (Robertson and Simmons 2013).

Participants gave their written consent beforehand, and approval was obtained from the local ethics committee. All participants completed the experiment at the same moment, in a behavioral experiment room with 30 isolated computers. At the beginning of the experiment, participants were informed that the five participants with the highest level of accuracy would be indemnified 20€, instead of 15€. We chose a difference in rewards in order to motivate participants, and the level of accuracy was calculated based on control trials.

### *Stimuli*

Stimuli were grey discs whose luminance slightly changed over time of presentation, as they were 800ms-videos of “twinkling” grey discs. Each video was made of 40 grey discs displayed 20ms each. Every disc was 220 pixels wide, had a homogeneous luminance, and was displayed in the middle of the screen on a dark grey background (luminance: 0.2). The borders of the disc were slightly smoothed to decrease the contrast between the screen luminance and the disc luminance. Importantly, the luminance level was the only parameter varying between videos. The average luminance of the video was either 0.54 ( $L_A$ ), 0.59 ( $L_B$ ), 0.65 ( $L_C$ ), 0.71 ( $L_D$ ) or 0.78 ( $L_E$ ). These five luminance levels were chosen so that the clearest luminance  $L_E$  was 20% lighter than average of the luminance range  $L_C$ . The other luminance values were chosen on a logarithmic scale, so as to take account for Weber Law (e.g.,  $\log(\frac{L_E}{L_D}) = \log(\frac{L_D}{L_C})$ ).

In each video, the luminance levels of the 40 discs were chosen in a Gaussian distribution centered on  $L_A$ ,  $L_B$ ,  $L_C$ ,  $L_D$  or  $L_E$  on a logarithmic scale. The variance of the Gaussian distributions was either low (*standard condition*, variance = .04) or high (*noisy condition*, variance = .08). For each level of luminance ( $L_A$  to  $L_E$ ) and condition (standard or noisy), we created five videos in which the order of the 40 discs was modified. Visual stimuli were displayed using Presentation (<https://www.neurobs.com/> 17.1 03.15.14).

**Visual task**

Two discs were successively presented and participants had to determine whether the second disc was more or less dark than the first one (Figure 1). To answer, they had to click on the side of a plus sign (i.e. second disc darker) or of a minus sign (i.e. second disc less dark). The sides of the plus and minus signs never changed, but were counterbalanced between subjects.

Figure 1.A presents an example of trial. The first disc was presented for 800ms, followed by 1000ms of delay, and then by the second disc displayed for 800ms. A response screen appeared immediately after the second disc, and subjects had up to 3000ms to answer. The inter trial interval lasted for 1500ms.

The task was designed to induce a time-order effect (TOE), whereby the perception of the first stimulus is biased toward the prior in ambiguous contexts (due to the delay between the two stimuli). Here the prior corresponded to  $L_C$ , which was the average luminance of the discs. Hence, with a TOE, the luminance of the first disc should be seen as closer to  $L_C$  than it actually is.

There were eight kinds of trials: two kinds of *identical TOE trials* where the two discs had the same luminance, four kinds of *different TOE trials* where the two discs had a different luminance, and two kinds of *control trials* where the first disc had the luminance of the prior ( $L_C$ ). These trials were pseudo-randomly presented during an experiment: every eight trial, each kind of trial had been presented.

*Identical TOE trials ( $L_A-L_A$ , or  $L_E-L_E$ )*

In these trials, the two discs displayed had the same luminance. According to the TOE, the perception of the first disc should be biased toward  $L_C$ . Hence, if two  $L_A$  discs (darker than the prior) are presented, the first disc should be perceived as clearer than it actually is, and so, the second disc should be perceived as darker than the first one (Figure 1.B). Conversely, if two  $L_E$  discs (clearer than the prior) are presented, the first disc should be perceived as darker than it actually is, and so, the second disc should appear clearer than the first one. To sum up, two  $L_A$  discs should be associated with the answer *darker*, whereas two  $L_E$  discs should be associated with the answer *less dark*. If there is no TOE, we should observe 50% of each kind of answers in each case.

*Different TOE trials ( $L_A-L_B$ ,  $L_B-L_A$ ,  $L_D-L_E$  or  $L_E-L_D$ )*

In these trials, two discs of different luminance were displayed. Depending on the order of presentation, the luminance comparison should be facilitated or harder. Indeed, if  $L_B$  is displayed before  $L_A$  ( $L_B$  is clearer than  $L_A$ ),  $L_B$  will be perceived as even clearer because it is biased toward the clearer prior  $L_C$ . Hence, the perceived difference in luminance will be increased, and the rate of correct answers will increase (Figure 1.B). As a contrary, if  $L_A$  is displayed before  $L_B$ ,  $L_A$  will



The six tasks were two *standard condition* tasks and four *noisy condition* tasks: the sensory noise was increased in the 1<sup>st</sup> disc in two tasks (*1<sup>st</sup>-noisy condition*), and in the 2<sup>nd</sup> disc in two tasks (*2<sup>nd</sup>-noisy condition*). The order of presentation of the tasks was counterbalanced between participants. Adding noise to the stimuli decreases sensory precision, but might also affect prior precision.

In the *1<sup>st</sup>-noisy condition*, the perception of the first disc should be even more biased toward the prior than in the *standard condition*. Indeed, the relative weight of prior on perception should be increased both by the decreased sensory precision and by the delay. Hence, the TOE should be increased as compared to the *standard condition*.

In the *2<sup>nd</sup>-noisy condition*, both the first and second stimuli should be biased toward the prior: due to the delay for the 1<sup>st</sup> stimulus, and due to the noisy luminance for the 2<sup>nd</sup> stimulus. Hence, the TOE should be decreased as compared to the *standard condition*.

### ***Statistical analyses***

Chance levels were determined using binomial tests, and comparison between observed mean and chance level were performed with one-sample Student t-test. Differences in performance and response times between a noisy condition and the standard condition were assessed using pairwise Student t tests. Correlations between performance and questionnaire scores (Autism spectrum quotient and Glasgow Sensory Questionnaire) were assessed using Pearson correlation test. Unanswered trials were discarded from the analyses.

Statistical analyses were performed using R (<http://www.r-project.org/>). Statistical threshold was set at  $p < .05$ , and multiple comparison corrections were realized using Bonferroni correction.

## **Results**

### ***Control trials***

There was 79% ( $\pm 16$ ) of correct answers in the training session.

During the six tasks, participants got 87% ( $\pm 7$ ) of correct answers for control trials, and had an average response time for correct answers was 384ms ( $\pm 106$ ). The accuracy for control trials was not different between conditions: 88% ( $\pm 10$ ) in the *standard condition*, 85% ( $\pm 7$ ) in the *1<sup>st</sup>-noisy condition*, and 88% ( $\pm 9$ ) in the *2<sup>nd</sup>-noisy condition*. The average response time was and response times did not differ between the three conditions (*standard condition*: 385ms ( $\pm 132$ ), *1<sup>st</sup>-noisy condition*: 387ms ( $\pm 114$ ), *2<sup>nd</sup>-noisy condition*: 380ms ( $\pm 107$ )).



***Time-order effect for identical stimuli***

Participants showed a TOE (Figure 2.A): they answered that the second one was darker than the first one in 82% ( $\pm 12$ ) of the cases when discs were dark ( $L_A$  darker than  $L_C$ ), and answered that it was clearer in 87% ( $\pm 12$ ) of the cases when discs were clear ( $L_E$  clearer than  $L_C$ ). These percentages are referred to as *biases for identical stimuli*, and were significantly different from chance level (65%) ( $L_A$  and  $L_E$ :  $p < 10^{-6}$ ).

The average bias for identical stimuli (mean of  $L_A-L_A$  and  $L_E-L_E$ ) was 84% ( $\pm 10$ ). Every subject had a bias above chance level, except for one participant who got a mean bias of 58%. The mean response time for these trials was 429ms ( $\pm 145$ ).

***Time-order effect for different stimuli***

Participants also showed a TOE for trials with different stimuli (Figure 2.C). Indeed, for dark discs, the percentage of correct answers was 61% ( $\pm 19$ ) (i.e. under chance level) when the presentation order was  $L_A-L_B$ , and 93% ( $\pm 6$ ) when the presentation order was  $L_B-L_A$ . For clear discs, the percentage of correct answers was 55% ( $\pm 20$ ) (i.e. under chance level) when the presentation order was  $L_E-L_D$ , 96% ( $\pm 5$ ) when the presentation order was  $L_D-L_E$ .

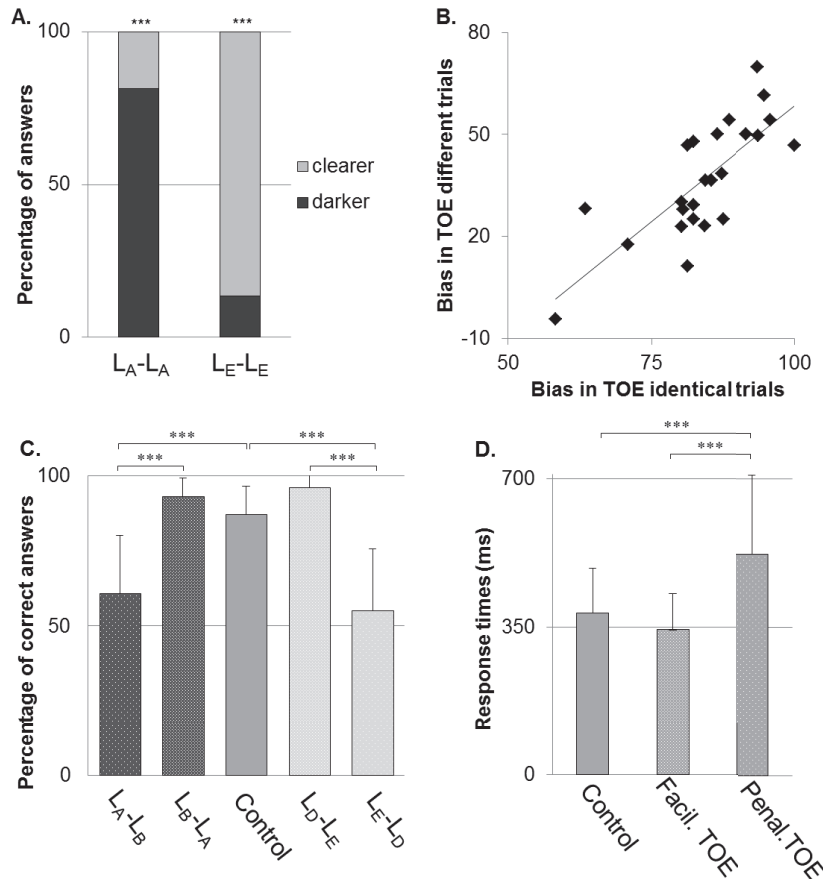
Facilitated TOE trials correspond to  $L_A-L_B$  and  $L_D-L_E$ , whereas penalized TOE trials correspond to  $L_B-L_A$  and  $L_E-L_D$ . The comparison of penalized trials to facilitated trials showed lower accuracy (58%  $\pm 16$  vs. 95%  $\pm 5$ ,  $p < 10^{-6}$ ) and longer response times (524ms  $\pm 186$  vs. 345ms  $\pm 85$ ,  $p < 10^{-6}$ ) (Figure 2.D). Accuracy in control trials was significantly lower than in facilitated TOE trials ( $p < 10^{-6}$ ) and higher than in penalized TOE trials ( $p < 10^{-6}$ ).

The perceptual bias can be calculated as the difference in accuracy between facilitated and penalized TOE trials for each luminance pair. Interestingly, the bias for different TOE trials was strongly correlated with the bias for identical TOE trials ( $r = .76$ ,  $p < 10^{-5}$ ) (Figure 2.B).

***Correlations with the AQ and GSQ***

Participants scored 16 ( $\pm 8$ ) at the Autism spectrum Quotient, and 57 ( $\pm 21$ ) at the Glasgow Sensory questionnaire. We tested correlations between the perceptual bias for different or identical trials, and the AQ (total score, and attention to details score) and the GSQ (scores for visual hyper- and hypo-sensitivities).

There were tendencies toward a positive correlation between the AQ score of attention to details and the perceptual bias in TOE different trials ( $r = .37$ ,  $p = .07$ ). However, the GSQ score did not correlate with the perceptual bias.



**Figure 2: Main accuracy and bias in the six tasks**

**A.** Percentage of answers indicating that the 2<sup>nd</sup> disc was clearer or darker than the 1<sup>st</sup> one, for two dark discs ( $L_A$ ), or two clear discs ( $L_E$ ).

**B.** Correlation between the two types of biases ( $r = .76$ ,  $p < 10^{-5}$ ).

**C.** Percentage of correct answers for the TOE different trials. The TOE can be seen with changes in accuracy depending on the presentation order (e.g.  $L_B-L_A$  easier than  $L_A-L_B$ ).

**D.** Mean response times for control trials, and for trials facilitated by the TOE ("Facil. TOE", e.g.  $L_B-L_A$ ), or penalized by the TOE ("Penal. TOE", e.g.  $L_A-L_B$ ).

\*  $p < .05$ , \*\*  $p < .005$ , \*\*\*  $p < .0005$ . Error bars correspond to standard deviations.

### Comparison of the three kinds of sessions

Participants performed similarly for control trials of the three types of sessions (*standard*:  $88\% \pm 10$ , *1<sup>st</sup>-noisy*:  $85\% \pm 7$ , *2<sup>nd</sup>-noisy*:  $88\% \pm 9$ ), and no differences in response times were observed (*standard*:  $385\text{ms} \pm 132$ , *1<sup>st</sup>-noisy*:  $387\text{ms} \pm 114$ , *2<sup>nd</sup>-noisy*:  $380\text{ms} \pm 107$ ).

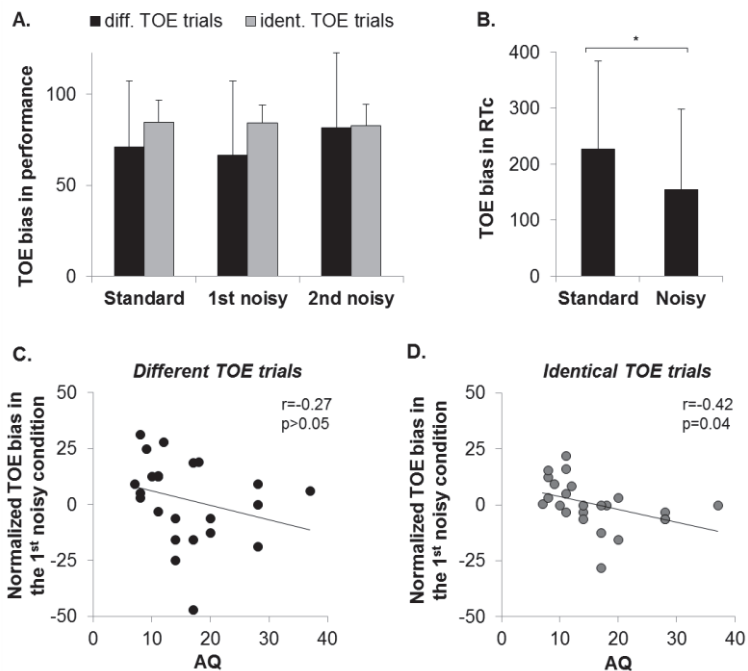
There was no effect of the type of session on the perceptual bias for identical TOE trials (Bias in *standard*:  $85\% \pm 12$ , *1<sup>st</sup>-noisy*:  $84\% \pm 10$ , *2<sup>nd</sup>-noisy*:  $83\% \pm 12$ ) or for different TOE trials (Bias in *standard*:  $36\% \pm 18$ , *1<sup>st</sup>-noisy*:  $33\% \pm 20$ , *2<sup>nd</sup>-noisy*:  $41\% \pm 20$ ).

The comparison of the bias in accuracy in the standard condition as compared to the noisy conditions (1<sup>st</sup> and 2<sup>nd</sup>-noisy conditions) showed no significant difference. The TOE bias can also be seen on response times. The bias in response time was decreased in the noisy conditions as compared to the standard condition ( $155\text{ms} \pm 126$  vs.  $227\text{ms} \pm 157$ ,  $p = 0.003$ ).

The effect of sensory noise on perceptual bias varied between participants, and we assessed whether between-subjects variations could be related to different levels of autistic traits.

To study the effect of sensory noise, we calculated the normalized TOE bias, corresponding to the difference in TOE bias between the *standard condition* and the *1<sup>st</sup>-noisy condition* or the *2<sup>nd</sup>-noisy condition*. We further assessed correlations between the AQ and the normalized TOE bias (reflecting how sensory noise changed the perceptual bias). The normalized TOE bias for the 1<sup>st</sup>-noisy condition and the AQ were negatively correlated for identical trials ( $r =$

-.42,  $p < .05$ ), but not for different trials ( $r = -.27$ ,  $p = .20$ ). The normalized TOE bias for the 2<sup>nd</sup>-noisy condition and the AQ were not significantly correlated. Finally, the normalized accuracy (in standard condition minus noisy condition) was not correlated with the AQ.



### Figure 3: Results for the three versions of the perceptual task

**A.** Mean bias for the different TOE trials (black) and identical TOE trials (grey) in the standard, 1<sup>st</sup>-noisy and 2<sup>nd</sup>-noisy conditions.

**B.** Mean bias in response times for correct answers for the standard and noisy versions of the task. The 1<sup>st</sup> and 2<sup>nd</sup> noisy versions are averaged and correspond to the noisy section.

**C-D.** Negative correlations between the AQ and the normalized TOE bias in the 1<sup>st</sup>-noisy version, for different (C) or identical (D) TOE trials.

*p*-values: \* $p < .05$ .

Error bars correspond to standard deviations.

## Conclusion

This new visual task elicited a time-order effect in control participants, both for stimuli of different luminance, and of similar luminance. We attempted to increase sensory noise in the first or second stimuli, in order to modulate the relative weights of sensory inputs and priors and to assess how it would affect perceptual decisions. However, adding sensory noise did not have the expected effect, maybe because the variance of the luminance distribution was not increased enough. Indeed, reducing sensory precision should have led to decreased accuracy and/or longer response times in control trials, but this was not observed. Increasing more the luminance variance would have resulted in too highly overlapping luminance between stimuli.

Besides, we had hypothesized that subjects with high autistic traits would be more sensitive to the effects of sensory noise, if they gave a higher confidence to sensory inputs. Yet, we found the inverse correlation: decreasing sensory precision in the first stimulus increased the relative prior weight in subjects with low AQ, but did not affect perceptual bias in subjects with higher AQ. We can hypothesize that in subjects with higher AQ, priors might have overfitted the noisy sensory context, resulting in decreased prior precision. Hence, decreasing both sensory and prior precisions would not have modified the relative precision balance.

Future work should try to increase more the variance of stimuli luminance, or to compare situations with longer versus shorter videos to modify the amount of accumulated evidence.

## Appendix 2: Testimonies on sensitivity by women with Asperger's syndrome

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*Laurie-Anne Sapey-Triomphe, Hassenia Mecheri*

### *Materiel et Méthodes*

#### ***Participant***

Vingt femmes diagnostiquées avec des troubles du spectre de l'autisme ont été incluses dans cette étude. Ces femmes étaient âgées en moyenne de 35,6 ans ( $\pm 8.5$ ), avec des âges variant de 20 ans à 53 ans. Elles ont été diagnostiquées par des psychiatres selon les critères du Manuel Diagnostique des Troubles mentaux [1], avant 2013, comme ayant un syndrome d'Asperger. Les participantes ont reçu leur diagnostic en moyenne à 35.6 ans ( $\pm 9.6$ ), les âges de diagnostic allant de 16.0 ans à 49.5 ans. Les questionnaires ont été remplis en moyenne 2,3 ans après avoir reçu un diagnostic officiel de syndrome d'Asperger.

En plus du diagnostic de syndrome d'Asperger, trois participantes ont eu un diagnostic de dépression, quatre de troubles anxieux, trois de haut potentiel intellectuelle, une de troubles obsessionnels du comportement, une d'hyperactivité et enfin une d'anorexie.

Les participantes ne présentaient pas de déficience intellectuelle et avaient le français comme langue maternelle. Dix participantes étaient sans emploi, 6 avec emploi et 3 étudiantes.

#### ***Procédure***

Cette étude comporte l'originalité d'avoir été initiée et menée par une personne ayant été diagnostiquée avec un syndrome d'Asperger. Le recrutement s'est fait via le site internet de l'investigatrice de l'étude. Les questionnaires ont été envoyés une semaine avant un entretien téléphonique, afin de permettre aux participantes de pouvoir préparer leurs réponses. Les réponses des participantes ont été enregistrées lors d'un entretien téléphonique (après accord écrit des participantes), puis retranscrites à l'écrit. Pour cinq d'entre elles, le recueil des réponses a été effectué par écrit, à cause de la gêne causée par le téléphone. Les entretiens téléphoniques duraient en moyenne deux heures.

### ***Instrument***

Les questionnaires ont été développés spécifiquement pour cette étude et comportent 134 questions. Ces questions ont été formulées par une femme avec syndrome d'Asperger en supposant qu'elles pourraient révéler des particularités sur les femmes avec SA. Les questions se déclinent en trois parties majeures, l'enfance, la puberté et l'âge adulte. La première partie, concernant l'enfance, aborde principalement des questions relatives à la sensibilité émotionnelle, sensorielle, au monde imaginaire, aux différentes manies, routines et stéréotypies rencontrées et au rapport aux autres. La seconde partie, sur la puberté, est organisée en questions concernant le rapport à son propre corps, le rapport aux autres filles et garçons, à la scolarité et enfin en une grande partie concernant les éventuels troubles annexes rencontrés. Enfin, la troisième partie, concernant l'âge adulte, comporte des questions relatives à la sensibilité émotionnelle, la sensorialité, le comportement, la vie sociale, la vie sentimentale, les enfants, le monde du travail et enfin le déroulement du diagnostic. Une conclusion de ce questionnaire est proposée avec des questions réflexives sur la philosophie de vie des participantes. La majorité des questions est accompagnée d'exemples entre parenthèses. Un exemple de question est « *Vous arrive-t-il d'avoir des sensations de surcharges sensorielles ? Si oui, dans quelles circonstances, quels lieux, avec quels déclencheurs ? (exemple : endroits fermés, surpeuplés, bruyants, etc... )* ».

Les questions étaient ouvertes, et donc sans limite de réponse. Vu l'exhaustivité du questionnaire, son analyse a été scindée en deux thèmes : un premier regroupant sensibilités sensorielle et émotionnelle, thème du présent article, et un second thème centré sur le développement de ces femmes avec SA dans un environnement social.

### ***Analyse***

Une analyse thématique a été effectuée pour traiter les réponses ouvertes des participantes. Afin de quantifier les réponses, des catégories de réponses ont été identifiées. Cette catégorisation des réponses a été faite indépendamment par deux auteurs, et lorsque le codage des types de réponses différaient, le point en question était discuté jusqu'à obtenir un consensus. Pour un grand nombre de questions, les réponses pouvaient simplement être catégorisées en *oui, non, je ne sais pas*. Les résultats de cette analyse thématique sont présentés comme des résumés qualitatifs, illustrés par des exemples jugés comme étant particulièrement représentatifs ou pertinents. Cet article vise donc principalement à témoigner sur le ressenti des femmes avec syndrome d'Asperger, grâce à des illustrations concrètes.

## Résultats

### 1. Sensibilité sensorielle

#### 1.1 Sensibilité sensorielle pendant l'enfance

Toutes les participantes ont indiqué posséder au moins un sens particulièrement hypersensible. Les modalités sensorielles les plus citées sont l'audition (15), la vision (13), le toucher (12), l'olfaction (10), et le goût (7). L'une d'entre elle note une sensibilité sensorielle quelque peu paradoxale : *« J'ai toujours eu une sensibilité assez développée mais pas de façon uniforme : je peux être très sensible à une texture mais ne pas ressentir le froid, par exemple »*.

#### **L'audition**

L'hypersensibilité auditive peut se traduire à plusieurs niveaux : *« J'entendais des sons qui étaient relativement faibles, et certains étaient comme amplifiés »*, et peut être accompagnée d'une hyperréactivité : *« Enfant, je pleurais dès qu'une moto passait, je ne supportais pas les applaudissements »* et d'une fatigue : *« J'entends tout, tout le temps, c'était et c'est fatiguant »*. Le caractère inattendu de la stimulation auditive potentialisait l'hyperréactivité : *« J'ai une hypersensibilité aux bruits soudains, inattendus, tranchants, ceux-ci me blessent les oreilles et me font accélérer le cœur »*.

#### **La vision**

Toutes les participantes rapportant une hypersensibilité visuelle soulignent des difficultés dues aux luminosités très vives : *« Mes yeux sont très sensibles à la lumière, la lumière trop vive, les jours ensoleillés me fatiguent »*, ainsi qu'aux variations de luminosité : *« Il ne faut pas qu'il y ait un néon scintillant au-dessus de moi »*.

#### **L'odorat et le goût**

L'hypersensibilité olfactive se présente comme une gêne quotidienne due à un envahissement olfactif : *« J'ai toujours eu beaucoup de difficultés avec les personnes trop parfumées, trop envahissantes olfactivement »*. Pour l'une des participantes, cette hypersensibilité est cependant un atout dans le monde social : *« Les parfums m'aidaient à identifier les gens »*.

L'hypersensibilité gustative apparaît liée à des habitudes alimentaires assez fixes : *« Je mangeais souvent la même chose parce que mon goût est très développé »*.

#### **Le toucher**

Les gestes quotidiens sont affectés par l'hypersensibilité tactile : *« Mon corps avait et a encore des réactions exagérées au contact physique, ainsi qu'au contact avec certains habits. Ça*

*gratte, ça pique, ça brûle, certaines étoffes me dérangent* ». L'hypersensibilité tactile dans les interactions sociales ressort tout particulièrement vu que l'ensemble des femmes rapporte détester les contacts avec autrui lorsque ceux-ci n'étaient pas bien maîtrisés et anticipés : « *Je n'aimais pas être prise par surprise, ça engendrait chez moi un sentiment de repli et de la frustration et je pouvais être violente* », « *Lorsqu'une personne me touchait sans m'avertir, cela me provoquait comme des douleurs sur la peau, ou des frissons électriques* ». Deux participantes soulignent n'apprécier que les contacts francs dans les rapports avec les autres : « *Je n'aime toujours pas qu'on me frôle, j'aime bien le toucher franc* ». Les difficultés liées aux contacts tactiles se retrouvaient dans la sphère familiale : « *Je reculais quand mes parents voulaient me faire un câlin* », ainsi qu'à l'école : « *Je n'aimais pas les rondes d'enfants parce qu'il fallait se toucher la main, mais je ne sais pas si c'est le contact physique ou si c'est parce que je ne comprenais pas ce qui se passait* ».

Une question interrogeait la résistance à la douleur et aux températures extrêmes lorsqu'elles étaient enfants. Six femmes ont déclaré qu'elles avaient une certaine insensibilité à la douleur et aux fortes et faibles températures : « *J'étais insensible à la douleur, ma tolérance était forte. Je n'avais jamais froid, j'étais toujours habillée légèrement je ne fermais pas les manteaux, je ne mettais jamais d'écharpe de bonnets, de gants ni de col roulé, d'ailleurs je ne supportais pas ça* ». Au contraire, cinq femmes rapportent être hypersensibles aux températures : « *J'étais trop sensible, je tolérais très mal la chaleur, et j'étais très frileuse* ». Enfin, huit participantes disent avoir une tolérance relativement paradoxale caractérisée par des hyper- et hypo-sensibilités : « *J'étais très douillette pour les petits bobos du quotidien, et très résistante pour les choses qui auraient dû me faire hurler de douleur* ». Ici encore, deux des participantes soulignent l'importance de la prédictibilité de ces sensations : l'une explique qu'elle était très sensible à la douleur, « *mais si on me provoque une douleur en me prévenant, je ne la sens presque pas* ». De même, un autre souligne : « *La douleur est insupportable quand elle est imprévue, l'effet de surprise est intolérable, plus que la douleur elle-même* ». Enfin, l'une des participantes ne se rappelle pas d'éléments particuliers concernant leur sensibilité à la douleur et à la température.

### ***1.2 Évolution de la sensorialité à l'âge adulte***

Seize participantes ont répondu à la question sur l'évolution de la sensorialité à l'âge adulte. Une participante déclare que sa sensorialité s'est aggravée à l'âge adulte, tandis que les quinze autres disent ne pas avoir constaté d'évolution. Cependant, sept d'entre elles remarquent une amélioration dans la gestion de leur sensorialité : « *J'ai des petits trucs pour gérer et j'arrive à m'en accommoder, mais il faut dire je n'ai pas le choix* ». Les stratégies développées consistent à éviter toute situation trop intense et à minimiser les états de

surprise : « *Je me protège en effaçant le plus possible l'inconnu* ». Concernant son hypersensibilité, l'une des femmes rapporte : « *Aujourd'hui, elle existe toujours mais je la canalise, pour ne plus la ressentir. Je me suis repliée et je me suis éteinte* ». L'ensemble des femmes disent subir cette sensorialité, sauf pour quatre d'entre elles qui l'utilisent comme un atout.

Concernant le toucher, quinze femmes ont indiqué que le toucher est toujours problématique à l'âge adulte, en particulier lorsqu'il implique des contacts physiques avec d'autres personnes : « *J'ai beaucoup de peine à toucher et être touchée et j'en souffre. Mon esprit voudrait mais mon corps refuse* ». Des stratégies ont été mises en place, par exemple : « *Je me mets en pilotage automatique, lorsque je sais que je vais devoir serrer des mains lors de réunion* ». Parmi ces femmes, sept précisent qu'elles parviennent à supporter les contacts physiques avec les personnes dont elles sont très proches (conjointes, enfants, et parents). Une fois encore, six femmes précisent que les contacts sont d'autant plus désagréables qu'ils sont imprévus : « *Je déteste encore plus que l'on me touche, sauf si je m'y attends* », « *Quand quelqu'un me prend dans ses bras contre mon gré et de manière inattendue, je me rigidifie comme un morceau de bois* ». Une autre participante dit apprécier la modalité tactile.

### ***1.3 Sensations de surcharge sensorielle***

Dix-sept femmes ont répondu à la question sur les surcharges sensorielles. Elles ont toutes déclaré avoir été fréquemment soumises à des sensations de surcharge sensorielle dans l'enfance ainsi qu'à l'âge adulte. Les deux éléments récurrents dans les témoignages sont la nature auditive du déclencheur, et la souffrance due à une certaine incompréhension de leur entourage.

Les déclencheurs cités sont généralement auditifs : « *C'était très souvent à cause des bruits, des cris des autres enfants à l'école, la cour de récréation était toujours très pénible pour moi, je redoutais ces moments où tout bougeait, tout était si bruyant, tout était si angoissant* ». L'une des participantes explique que des crises survenaient « *lorsque j'étais surprise par le moindre bruit soudain, ce qui me faisait mal* ». Une femme témoigne d'autres déclencheurs : « *Certaines lumières m'agressent et ça peut me mettre en colère, les odeurs me gênent énormément* ». Quatre femmes expliquent que ces sensations d'envahissement surgissent particulièrement dans les contextes sociaux. Enfin, ces sensations d'envahissement sont souvent provoquées par un changement, tel que « *le changement de climat* », « *un nouvel emploi* », ou encore « *un retard des transports en commun* ». L'une des femmes précise qu'étant enfant elle avait des difficultés à identifier clairement ce qui animait ces sensations : « *Je ne pouvais pas*



*savoir quels étaient les déclencheurs, je me sentais envahie, agressée* », mais elle note une meilleure clairvoyance à l'âge adulte.

Ces sensations peuvent se provoquer « *des crises de larmes, des symptômes physiques aussi (maux de ventre, vertiges, maux de tête...)* », de la colère voire de la violence « *Je pouvais être submergée au point de saturer et je réagissais violemment. J'étais très bagarreuse, j'allais frapper les personnes qui étaient à la source de cette charge sensorielle* », de l'isolement « *Je réagissais avec le mutisme, je ne disais plus un mot, parfois je restais figée et immobile* », une fuite, ou une combinaison de réactions « *Je les exprimais par des pleurs, mutisme également, angoisses, refus de s'alimenter, fuite dans ma chambre* ». A l'âge adulte, ces réactions sont mieux canalisées que dans l'enfance.

#### **1.4 Synesthésie**

Neuf femmes sur dix-sept ont indiqué être synesthètes, les autres n'ayant pas répondu à cette question. L'un des témoignages est particulièrement précis : « *Lorsque j'entends un son je peux voir des formes ou des couleurs ou même une sorte de film intérieur comme un kaléidoscope. Cela peut être des foulards : des traînées de couleurs, et parfois c'est un envahissement par une couleur en particulier de tout mon champ visuel. Le bleu est associé à la musique baroque pour moi. Lorsque je me sens bleue c'est une sensation agréable et bucolique* ». Toutes les modalités sensorielles sont citées, « *Ce que j'entends se colore, a une saveur, ce que j'observe aussi a une sonorité, une saveur* », « *En entendant certains sons, je vois des couleurs ou des types de paysages, ou parfois je ressens des différences de températures (je peux me sentir engloutie dans un lac gelé)* ». Les synesthésies entre mots et couleurs sont évoquées par 4 participantes. Enfin, l'une des femmes applique sa synesthésie au monde social : « *J'associe une personnalité à certains nombres ou chiffres, donc j'ai des chiffres qui me sont sympathiques (5, 7, 9), ou hostiles (4 et 8), certains me mettant mal à l'aise (11), et d'autres plus chaleureux (12 et 13)* ».

#### **1.5 Sensorialité et expertise**

Il était demandé à ces femmes si elles avaient un talent particulier, en lien avec leur sensorialité. Trois femmes ont rapporté avoir l'oreille absolue, cinq autres une très bonne mémoire auditive (2), photographique (2), ou spatiale (1), deux ayant des talents marqués pour le dessin, deux ayant des talents d'écriture et d'analyse, et l'une ayant développé une expertise sensorielle : « *L'odorat et le goût sont mes atouts, je fais partie d'un panel d'experts en dégustation pour les vins. J'apprécie énormément d'avoir un sens de l'odorat et du goût bien développé, c'est très utile pour mon métier de caviste* ». Enfin, cinq femmes ont estimé qu'elles n'avaient pas un talent dans un domaine spécifique.

## **2. Sensibilité émotionnelle**

### **2.1. Identification des émotions**

#### ***Enfance***

Seules deux femmes rapportent avoir été capables de clairement nommer leurs émotions étant enfant. Les autres femmes avaient des difficultés : « *Je savais identifier les émotions comme étant agréables ou désagréables, les nommer plus difficilement car bien souvent les émotions me submergeaient avant que j'ai eu le temps de les catégoriser* ». Le ressenti des émotions est bien présent, mais c'est l'identification de cette émotion qui est problématique : « *Je crois que j'ai toujours eu du mal à dire ce que je ressentais. Je savais quand j'étais en colère ou quand j'étais triste, mais pour les plus compliquées, ce n'était pas facile, j'extériorisais très peu. Donc je ressentais une sorte de bouillonnement sans que ça ne sorte* ». Cette incompréhension se traduit par une peur pour l'une des participantes : « *Je ressens toujours des émotions internes "violentes", et c'est ce qui me fatigue, parce que je n'arrive pas à les identifier, cela me dépasse et me fait peur* ».

#### ***Age adulte***

Dix-neuf femmes ont répondu à la question interrogeant sur l'évolution de leur sensibilité émotionnelle à l'âge adulte. Cinq femmes ne pensent pas avoir vu d'évolution depuis leur enfance, tandis que quatorze femmes notent une évolution : « *J'arrive mieux à les identifier car il y'a une grande palette pour nommer les émotions. Il n'y a pas qu'un mot* ». Cette amélioration est en partie due à l'utilisation de pictogrammes, à la lecture de livres, à l'aide par des spécialistes, au théâtre, à l'écriture, à la sophrologie ou à d'autres formes de développement personnel. Par exemple, l'une des femmes les identifie mieux grâce à l'écriture : « *Pour identifier les émotions, il faut que j'écrive tout ce que j'ai ressenti pour que je sache, il me faut faire une analyse approfondie, après coup, toute seule* ». Bien qu'elles parviennent désormais à les identifier, elles ont toujours des difficultés pour les gérer, et recherchent « *une certaine distanciation aux émotions* » : « *Le fait d'être devenue adulte m'a permis de prendre une distance avec ce qui me perturbe* ». Les stratégies utilisées sont la fuite, l'autodérision, ou de les cacher : « *Je porte aussi un masque pour gérer et me protéger* ».

### **2.2 Expression des émotions**

Une seule participante rapporte ne pas avoir de difficultés pour exprimer ses émotions. Huit femmes ont indiqué qu'elles ne parvenaient pas à exprimer leurs émotions, sous aucune forme « *Enfant, je ne les exprimais ni verbalement, ni non verbalement. Je restais assise où on*

*m'avait installée et je regardais des trous dans l'air, le regard fixe* ». L'expression de ces émotions nécessite un certain temps d'adaptation : *« Je reste "figée", parce que je ne les décède pas, mais ensuite, j'y réfléchis et je peux plus ou moins les exprimer, "toute seule" »*. Neuf femmes indiquent exprimer leurs émotions non verbalement, par des crises d'angoisse (2), par écrit (2), par la colère et l'excès (2) ou par des pleurs (3). Deux autres femmes indiquent les exprimer uniquement dans l'excès *« Dans le cas d'une émotion joyeuse je devenais très excitée, parfois un peu brusque, et dans le cas d'une émotion négative je détruisais des choses ou me faisais du mal, faute de pouvoir en faire aux autres »*.

### **2.3 Ressenti des émotions**

Seules deux participantes ont indiqué que leurs émotions pouvaient être nuancées, tandis que les 18 autres ont rapporté qu'elles étaient de type « tout ou rien » : *« Je fonctionne sur le mode binaire ! Elles sont du type tout ou rien, je ne connais pas le juste milieu »*.

Interrogées sur le fait d'être plutôt hypersensibles ou plutôt coupées de leurs émotions, seules 16 participantes ont répondu. Trois femmes ont indiqué être plutôt coupées de leurs émotions, et six autres se disent hypersensibles : *« J'ai toujours eu de la peine avec les émotions trop fortes, parfois je les éprouvais comme de l'agression envers moi et je n'en comprenais pas le but »*. Sept participantes rapportent que, paradoxalement, elles semblent coupées de leurs émotions malgré une hypersensibilité émotionnelle : *« J'étais très sensible, mais cela ne se voyait pas forcément car je présentais souvent une image impassible, très calme et silencieuse. À l'intérieur ce pouvait être la tempête, mais à l'extérieur cela ne se remarquait pas, car je ne laissais pas grand-chose transparaître »*. Enfin, l'une des femmes a tenu à préciser : *« Souvent on présente les autistes comme coupés de leurs émotions, mais pas du tout dans mon cas, je n'arrive pas à identifier les émotions dans l'instant, je suis submergée et en plus, mes sens sont toujours tous en éveil, donc au moindre changement, je suis troublée. Tout fonctionne mais je n'arrive pas à détailler ce qui se passe, donc je panique, et la seule façon de me raccrocher à l'instant, c'est de mettre en marche ma "logique", cela me calme, pour un temps, parce qu'ensuite, je suis comme épuisée »*.

### **2.4 Ressentis face aux émotions d'autrui**

#### **Enfance**

Neuf participantes ont rapporté un ressenti fort des émotions d'autrui, tout en ne sachant pas les identifier et ne sachant pas comment réagir *« Je ne savais pas comment me comporter face aux émotions d'autrui, ni quoi faire, ni quoi dire »*, ce qui entraînait une certaine culpabilité : *« Je*

*me sentais un peu bête, ma mère me disait que j'étais insensible, mais je ne me sentais pas insensible* ». L'une des participantes avait besoin de temps pour les comprendre : « *Je réagissais à retardement et j'étais donc très loin de mes émotions réelles, j'attendais, j'observais, je paniquais à l'intérieur et mon cerveau devenait purement intellectuel de façon à ne pas m'effondrer* ».

Six participantes ont dit se sentir généralement indifférentes face aux émotions des autres, à moins que cela ne les affecte personnellement : « *Je n'étais pas vraiment consciente des émotions des autres. Cela n'entrait presque jamais en ligne de compte dans mes raisonnements, sauf quand l'émotion d'autrui s'imposait à moi comme un obstacle ou une source d'incompréhension qui m'empêchait d'avancer* ». L'une d'entre elle a précisé avoir un comportement indifférent, malgré un grand ressenti émotionnel : « *En apparence j'y étais assez imperméable, j'avais toujours l'air distante et indifférente, mais intérieurement j'avais le sentiment d'être une éponge* ».

Enfin, quatre participantes estiment qu'elles étaient hypersensibles aux ressentis des autres, tandis que la dernière participante a indiqué qu'elle préférerait fuir les ressentis émotionnels des autres en se réfugiant dans sa « bulle ».

### ***Age adulte***

À l'âge adulte, les réactions face aux émotions des autres demeurent toujours problématiques.

Trois participantes expliquent être facilement submergées par les émotions d'autrui, tandis qu'une autre dit être fatiguée par leurs émotions. Sept autres essayent de prendre de la distance, physiquement ou psychologiquement, en tentant d'intellectualiser la situation : « *Je réagis de manière analytique, je n'arrive pas à réconforter par un geste, mais j'essaie de comprendre pourquoi la personne réagit ainsi, et ça peut être pas mal car mon regard apporte une façon plus distanciée moins émotionnelle* ». Huit femmes tentent d'intervenir auprès de la personne ayant ces émotions, mais ces manifestations restent discrètes et compliquées à gérer « *Ce n'est pas par désintérêt mais c'est que je n'y arrive pas. Je vais rester discrète, je vais essayer peut-être de dire quelque chose mais c'est souvent maladroit ou inapproprié* ». L'une des participantes souligne un certain dilemme dans l'attitude à adopter entre ce qu'elles sont supposées faire selon les codes sociaux appris (par exemple, mettre une main sur l'épaule), et ce qu'elles aimeraient qu'on leur fasse si elles étaient dans la situation de la personne (par exemple, partir et laisser la personne seule). Une autre participante essaye d'être à l'écoute dans les situations de détresse des autres, tout en se sentant désemparée. Enfin, deux participantes estiment bien réussir à gérer les ressentis d'autrui et à se comporter de manière appropriée. L'une conclut en expliquant : « *Les collègues me disent que je suis le ciment social de l'équipe et que j'ai une bonne qualité d'écoute, c'est quand même un comble pour une autiste !* ».

## 2.5 L'empathie

Sept participantes ont témoigné ressentir de l'empathie, et quatre d'entre elles ont précisé avoir observé une nette amélioration depuis leur enfance « *Je suis empathique, mais enfant j'étais en souffrance car je ne savais pas* ». L'une d'entre elles précise « *Normalement l'empathie est plutôt intuitive, moi, j'ai dû l'apprendre* ». Trois autres participantes se questionnent sur leur capacité à être empathique : « *J'ai toujours du mal à comprendre pourquoi ils ressentent ce qu'ils ressentent, et je ne fais pas de lien avec ce que moi j'ai pu vivre avant* ». Cinq autres estiment qu'il est très difficile d'être véritablement empathique si on n'a pas vécu précisément la même situation « *Je pense que c'est possible [d'être empathique] si on a déjà vécu la situation de la personne en question. Si on ne l'a pas vécue, on ne peut pas ressentir les émotions* ». Trois participantes précisent qu'il n'y a pas besoin d'être empathique quand il y a une solution concrète. Par exemple, au sujet de son neveu de 6 ans qui va avoir un pacemaker, l'une d'entre elle explique « *Je me dis que ce n'est pas grave. Je suis rationnelle pour le coup, il y a une aide technologique donc il va aller mieux* ». Enfin, une dernière pense manquer d'empathie et dit souffrir de ne pas savoir comment réagir « *Je n'aime pas que les gens me parlent de leurs soucis de santé car je ne sais pas quoi leur dire, à part leur donner des noms de spécialistes* ». Une participante n'a pas répondu à cette question car elle ne connaissait pas la définition de l'empathie.

## 3. L'imprévu

### 3.1. Réactions face aux changements et imprévus

Toutes les participantes ont rapporté avoir de grandes difficultés à supporter les changements et les imprévus, à l'exception d'une participante qui dit avoir seulement besoin d'un temps d'adaptation maintenant qu'elle est adulte. Depuis l'enfance, les problèmes liés aux imprévus ont diminué pour toutes les participantes, car elles ont développé des stratégies pour limiter ces situations : « *Quand j'étais enfant, c'était mes parents qui géraient et qui les provoquaient, j'étais obligée de suivre. Aujourd'hui, c'est moi qui ai le contrôle, donc je peux mettre des stratégies d'anticipation. Par contre quand ça arrive sans que je ne le voie venir, je me retrouve très démunie* ». Elles décrivent les imprévus comme étant désastreux, et source d'anxiété, voire de colère : « *Je n'ai jamais supporté les changements, cela me stresse énormément. Lorsque je me suis fait une vision imagée de ce qu'il faut faire, ou de ce qui va suivre et qu'une personne vient modifier mon programme, cela me bouleverse, il me faut du temps pour essayer de m'adapter* ». Les réactions face aux imprévus sont souvent mal comprises par les proches, comme en témoigne une des femmes : « *Sans prévenir, mon mari m'a offert des*

*chocolats en revenant du travail, et m'a dit de m'habiller pour filer au restaurant. Cela a déclenché une crise de larmes, d'angoisse et de cris car ce n'était pas prévu* ». L'une des participantes dit essayer parfois d'anticiper certains changements : *« D'un côté je n'aime pas changer mes habitudes, ça me fatigue et ça me stresse, surtout les imprévus. D'un autre côté, je me rends bien compte que la vie est faite de changements perpétuels, donc je m'oblige quelque part à accepter ce changement. Je vais préférer l'anticiper pour avoir un certain contrôle dessus »*. De la même manière, trois autres participantes expliquent être capables de gérer des changements, à condition qu'ils ne soient pas imprévus *« Je n'ai pas de mal à changer mes habitudes si c'est moi qui le décide, par contre si on me l'impose, je n'aime pas du tout »*.

### **3.2. Imprévus et comportements répétitifs**

Interrogées sur les situations dans lesquelles leurs stéréotypies étaient amplifiées, les femmes ont expliqué que cela survenait principalement dans les situations de stress, d'émotions fortes, ou d'imprévus : *« Dès qu'un imprévu arrive, je panique, je bouge mes doigts, je me balance, et je pense à mon obsession »*. Les imprévus génèrent un besoin de contrôler les sensations intérieures, ce qui peut être réalisé grâce aux stéréotypies. La minimisation des variations et changements se retrouve dans leurs routines et ce qu'elles qualifient comme des manies : *« Je passe deux à trois heures chaque jour à écrire ce que je vais faire dans la journée et je n'aime pas lorsque les choses identiques ne sont pas symétriques »*. Sur son quotidien étant enfant, l'une d'entre-elles précise *« Tout devait être planifié à la base, rien ne devait être imprévu »*.

## Appendix 3: Publication list

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### Articles included in the thesis

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- ◆ **Sapey-Triomphe L.A.**, Moulin A., Sonié S., Schmitz C. The Glasgow Sensory Questionnaire: validation of the French version and refinement of sensory profiles of people with high Autism Spectrum Quotient. *Article in minor revisions in the Journal of Autism and Developmental Disorders (JADD)*. ▷ [Study I](#)
- ◆ **Sapey-Triomphe L.A.**, Hénaff M.A., Sonié S., Mattout J. & Schmitz C. Adults with autism tend to undermine the hidden environmental structure: evidence from a visual associative learning task *Article submitted in JADD*. ▷ [Study II](#)
- ◆ **Sapey-Triomphe L.A.**, Sanchez G., Hénaff M.-A., Sonié S., Schmitz C., Mattout J. Behavioral evidence for a maladaptive perceptual inference in autism. *Article about to be submitted*.  
▷ [Study III](#)
- ◆ Three other articles are in preparation:
  - (1) fMRI study ▷ [Study IV, part 1](#)
  - (2) MR spectroscopy study ▷ [Study IV, part 2](#)
  - (3) Testimonies from women with Asperger syndrome on sensitivity ▷ [Appendix 2](#)

### Articles not included in the thesis

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- ◆ **Sapey-Triomphe L.A.**, Centelles L., Roth M., Fonlupt P., Hénaff M.A., Schmitz C., & Assaiante, C. (2016). Deciphering human motion to discriminate social interactions: a developmental neuroimaging study. *Social Cognitive and Affective Neuroscience*. <https://doi.org/10.1093/scan/nsw117>
- ◆ **Sapey-Triomphe L.A.**, Heckemann R. A., Boublay N., Dorey J.M., Hénaff M.-A., Rouch I., Padovan C., Hammers A., Krolak-Salmon P.; Alzheimer's Disease Neuroimaging Initiative. (2015). Neuroanatomical correlates of recognizing face expressions in mild stages of Alzheimer's disease. *PLoS One*, 10(12), e0143586. <https://doi.org/10.1371/journal.pone.0143586>
- ◆ Kumfor F.\*, **Sapey-Triomphe L.A.\***, Leyton C. E., Burrell J. R., Hodges J. R., & Piguet O. (2014). Degradation of emotion processing ability in corticobasal syndrome and Alzheimer's disease. *Brain: A Journal of Neurology*. <https://doi.org/10.1093/brain/awu246>  
\* co-first authors. Paper of the month and Editor's choice. Cover front of Brain.

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## Book chapters

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- ◆ **Sapey-Triomphe L.A.** “Le cerveau face à l'imprévu” (The brain dealing with unexpectedness), in the French book *L'imprévu: infortune ou opportunité?*, under the supervision of Pr Frydman and Dr Flis-Trèves. Editions PUF (2016).
- ◆ **Sapey-Triomphe L.A.** Preface, in the French book *Asperger et fière de l'être*, by Alexandra Reynaud. Editions Eyrolles (2017).

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## Conference posters

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- ◆ **Sapey-Triomphe L.A.,** Sanchez G., Sonié S., Schmitz C. & Mattout J. Prior construction and update in Autism Spectrum Disorders : a tactile perceptual task. *Poster/abstract for IMFAR conference 2016 (USA)*.
- ◆ **Sapey-Triomphe L.A.,** Sanchez G., Sonié S., Schmitz C. & Mattout J. Disentangling computational hypotheses on altered perceptual decisions in Autism: a behavioral study. *Poster/abstract for OHBM conference 2016 (USA)*.
- ◆ **Sapey-Triomphe L.A.,** Sanchez G., Sonié S., Schmitz C. & Mattout J. Assessing tactile perceptual inference and learning in autism spectrum disorders. *Poster/abstract for IMFAR conference 2015 (USA) and OHBM conference 2015 (USA)*.
- ◆ **Sapey-Triomphe L.A.,** Centelles L., Roth M., Fontlupt P., Hénaff MA., Assaiante C. & Schmitz C. Neurofunctional correlates of social interaction understanding during development. *Poster/abstract for OHBM conference 2015 (USA)*.
- ◆ **Sapey-Triomphe LA.,** Centelles L., Roth M., Fontlupt P., Hénaff MA., Assaiante C. & Schmitz C. Deciphering human motion to discriminate social interactions : functional connectivity changes across development. *Poster/abstract for OHBM conference 2014 (Germany)*.
- ◆ **Sapey-Triomphe L.A.,** Hénaff MA., Sonié S., Mattout J. & Schmitz C. Perceptual learning strategies in autism spectrum disorder. *Poster/abstract for EMBO conference 2014 (France)*.



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## Oral presentations on this PhD work

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- ◆ **Mathematic seminar – Biology month (2017)**: The predictive brain (Lyon, ENS, 1h30).
- ◆ **Lyon “Parent time” (2017)**: Autism, another perception of the world (Lyon, Lyon Public library, 2h).
- ◆ **Women and Science evening (2016)**: Presentation of my thesis project in Ted-X format (Paris, Pasteur Institute, 500 persons: [link](#)).
- ◆ **World Autism Day (2016)**: Sensory peculiarities in people with autism spectrum disorders (Villeurbanne, Palace of Labour, 120 persons, 1h).
- ◆ **Lyon Science Festival (2016)**: Presentation of my thesis in 3 minutes (Lyon, ENS, 300 persons)
- ◆ **GYPSY XV<sup>th</sup> congress (2015)**: Presentation of my thesis project (Paris, St Pères Medical School, 1200 persons).
- ◆ **Le Progrès Innovation Trophies (2015)**: Presentation of my thesis in 3 minutes (Lyon, ENS, 500 persons).
- ◆ **Three Minute Thesis contest (2015)**: Presentation of my thesis in 3 minutes (Lyon, Lyon University, 300 persons: [link](#); and Nancy, Prouvé Center, 800 persons: [link](#)).
- ◆ **CRA conference (2015)**: An atypical sensory perception: which specificities in Autism Spectrum Disorders (Bron, Autism Resource Center, 80 persons, 1h).
- ◆ **Oral communications in media (2015-2017)**: Interviews about my thesis for newspapers (21, e.g. [link](#)), national TV (2) and radio (5), Cortex Mag website ([link](#)) and UNESCO website.

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## Awards and fellowships received during the PhD

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- ◆ **2013**: PhD fellowship from the French Ministry of Higher Education and Research.
- ◆ **2015**: « Three Minute Thesis » 1<sup>st</sup> price (Lyon University). *Ranked 2<sup>nd</sup> for the internet price at the national level.*
- ◆ **2016**: L’Oréal-UNESCO fellowship for Women and Science (France). *Ranked 1<sup>st</sup> at the national level (>1000 candidates).*
- ◆ **2017**: Candidate selected to represent France for the *International Rising Talent Awards* in which 60 countries were involved. Ranked 16<sup>th</sup> internationally (the 15 first were awarded).