Sorbonne Université

Ecole Doctorale Cerveau Cognition Comportement (ED3C)

Institut du Cerveau et de la Moelle épinière

« PICNIC Lab »

Les fonctions cognitives du cortex visuel dans la cécité précoce

Cognitive functions of the visual cortex in the early blind

Par Sami ABBOUD

Thèse de doctorat de Neurosciences

Dirigée par Laurent COHEN

Présentée et soutenue publiquement le 26/04/2018

Devant un jury composé de :

M. Olivier COLLIGNON	PU, Université Catholique de Louvain	Rapporteur
M. Olaf HAUK	DR, University of Cambridge	Rapporteur
M. Marius PEELEN	PU, Radboud University Nijmegen	Examinateur
M. Richard LEVY	PU-PH, Sorbonne Université	Examinateur
M. Laurent COHEN	PU-PH, Sorbonne Université	Directeur

This page has been intentionally left blank

Table of contents

Acknowledgments iii
Abstract v
Résumé vi
List of publications vii
Abbreviations viii
1. Introduction 1
1.1. Blindness – definition 2
1.2. Behavioral consequences of blindness 3
1.2.1. Perception 4
1.2.1.1. Tactile 4
1.2.1.2. Auditory 5
1.2.1.3. Olfactory & Gustatory 6
1.2.1.4. Beyond the traditional senses 7
1.2.2. High-order cognition 7
1.2.2.1. Numerical skills and language 7
1.2.2.2. Executive functions 7
1.2.2.3. Memory 8
1.2.2.4. Attention 8
1.3. Functional recruitment of the visual cortex 9
1.4. Early evidence for a functional role 10
1.5. Specialized functional recruitment 10
1.5.1. Somatosensory processing 11
1.5.2. Auditory processing 12
1.5.3. Modality-independent perceptual processing 14
1.5.4. Higher-order processing 16
1.5.5. Language processing 19
1.5.6. Other symbolic representations 22
1.5.7. Long-term memory 22
1.5.8. Executive functions 25
1.6. Connectivity of the visual cortex 26
1.7. Summary and thesis outline 28
2. Cognitive functions of the visual cortex in the blind 31
2.1. Distinctive expansion of cognitive networks into the visual cortex in the blind 31
Abstract 33
2.1.1. Introduction 34
2.1.2. Materials and methods 35
2.1.3. Results 44

2.1.4. Discussion 52
2.1.5. Supplementary information 57
2.1.6. References 60
2.2. Innate connectivity of visual cortex 64
2.2.1. Hypothesis and analysis 64
2.2.2. Results 65
2.2.3. Discussion 68
2.2.4. Methods 70
2.3. Limitations and perspectives 72
3. Electrophysiological investigation of language 75
3.1. Semantic coding in the visual cortex of the early blind 75
Abstract 77
3.1.1. Introduction 78
3.1.2. Materials and Methods 80
3.1.3. Results 86
3.1.4. Discussion 94
Author Contributions 97
Acknowledgments 97
3.1.5. Supplementary information 98
3.1.6. References 102
3.2. Perspectives 105
Phonemic category discrimination 105
Oscillatory activity 106
Resting-state 107
4. General discussion 109
4.1. Thesis overview 109
4.2. Computation in the blind visual cortex 110
4.3. Function-connectivity correspondence 112
4.4. General perspectives 114
4.5. Conclusion 117
References 118
List of figures 132
Appendix A: A lateral-to-mesial organization of human ventral visual cortex at birth 133

Acknowledgments

First and foremost, I would like to thank Laurent Cohen for his dedication, patience and the countless hours of enriching discussion. I feel that the past 4 years were a true exchange where he was always available, physically and mentally, to contribute and criticize, to teach and learn, all the while giving me the liberty to explore and discover on my own. Laurent, I learned a lot from you and I profoundly appreciate your investment in me.

I would also like to thank Denis Engemann, which during the past year was a second mentor to me. He exposed me to the (complex) world of time-resolved neural dynamics and tried to show me that there is life beyond the BOLD signal. This dissertation cannot entirely reflect our lengthy discussions and arguments that deepened my understanding of brain dynamics and methods alike.

I wish to express my gratitude to current and past PICNIC lab members that gave me such a warm welcome upon arrival and walked me through the particularities and peculiarities of France. Florence, for numerous discussions on science, statistics, the visual word-form area but no less for your companionship and genuine care. Camille, for being Camille, for always being there to help and for spreading good energies around the lab. Tal, for your interest, care and support. Kasia, for the lovely scientific discussions and even lovelier discussions over lunch. Jaco and Jean-Remy, for brain-related brainstorming. Fede, for his wizardry. Lionel, for his sharp scientific instincts and constructive approach. Paolo, Imen, Diana, Mariam, Melanie, Athena, Pierre, Caroline, Bertrand, Pauline, Nadia, Cecile and little Arielle, for creating such a lovely working environment. Thank you for the fun, the science, and all the cakes!

I would also like to thank my collaborators that contributed from their mental capacity to my scientific upbringing. Ghislaine Dehaene-Lambertz and Pablo Barttfeld with whom I ventured into the realm of babies. Stanislas Dehaene for contributing from his busy resources to discuss ideas and results. Norman Sabah and Avinoam Safran for the work on vision restoration that did not make it to this dissertation, Christophe Pallier with whom it is always interesting to discuss. Nathalie George, Denis Schwartz and their team at the CENIR for the support in the conception and analysis of the MEG study. Christophe Gitton for teaching me how to get MEG signal from innocent subjects and Celine Cluzeau for her dedication and organization that allowed recruiting those subjects. Eric Bardinet and Jérôme Yelnik with whom we explored the thalamus. Ella Striem-Amit for insightful discussions and her valuble input. Mario Chavez for his support in analysis conception, and Jean Daunizeau that showed me the path towards Bayesian statistics.

I would like to thank my jury members, Olivier Collignon and Olaf Hauk for accepting to review this work, and Marius Peelen and Richad Levy for serving in my jury. I look forward to discuss my work with you during the defense.

I extend my appreciation to Jose-Alain Sahel and Amir Amedi for the initial push that conceived this project and secured part of its funding, and the “Leshanot Chaim” foundation for their part of the funding that finally allowed me to embark on this journey.

I am happy to thank the Ajités for their contribution to my integration in the institute and all the fun activities they organize. Especially so, Morwena whom I trust to make sure good things keep on happening and Alizée, for reasons beyond the scope of this section. ehem.

Un grand merci aux parents de Laurène, qui m’ont accueilli comme l‘un d’entre eux et m’ont soutenu même quand je faisais l’asocial en travaillant sur cette thèse.

To my friends, that live far away, you did your best to be present.

To my family, for without their continuous support and unconditional love, my life would have been less worthy.

Finally, to the special person that was by my side and will stay there for years to come.
(oui حبيبي, c’est toi)

Thesis starts there ---->

Abstract

Blindness early in life leads to major changes in the functional architecture of the brain. The occipital lobes, no longer processing visual information, turn to processing auditory and tactile input and high-order cognitive functions such as language and memory. This functional reorganization offers a window into the influence of experience on brain development in humans. We studied the outcomes of this reorganization and its potential precursors. First, we used functional magnetic resonance imaging (fMRI) in order to delineate regions in the visual cortex according to their sensitivity to high-order cognitive functions. Then, using functional connectivity, we demonstrated distinct connections from those regions to the rest of the brain. Crucially, we found a functional correspondence between the visual regions and their connected brain networks. Then, using functional connectivity in neonates, we provided preliminary evidence in support of the proposition that innate connectivity biases underlie functional reorganization. Second, we focused on language, one of the reorganized functions in blindness, and used magnetoencephalography (MEG) to investigate verbal semantic processing. We found temporally equivalent but spatially different activation across the blind and the sighted. In the blind, the occipital cortex had a unique contribution to semantic category discrimination. However, the cerebral implementation of semantic categories was more variable in the blind than in the sighted. Our results advance the knowledge about brain reorganization in blindness and contribute to the understanding of the general role of sensory experience in development.

Résumé

La cécité précoce induit des modifications majeures dans l'architecture fonctionnelle du cerveau. Les lobes occipitaux ne traitent plus l'information visuelle mais vont désormais traiter les signaux auditifs et tactiles et participer à des fonctions cognitives telles que le langage et la mémoire. Cette nouvelle organisation fonctionnelle nous permet de mieux comprendre l'influence de l'expérience sensorielle sur le développement cérébral. Nous avons étudié cette réorganisation et certains de ses possibles déterminants. Tout d'abord, nous avons utilisé l'imagerie par résonnance magnétique fonctionnelle (IRMf) pour identifier les régions du cortex visuel activées par différentes fonctions cognitives. Nous avons également montré que chacune de ces régions est fonctionnellement connectée au réseau cérébral qui sous-tend la fonction correspondante chez les sujets sains. Puis, nous avons réalisé une étude de la connectivité fonctionnelle chez des nouveau-nés, qui suggère que la connectivité innée du cortex visuel guide la réorganisation observée chez les aveugles. Ensuite, grâce à la magnétoencéphalographie (MEG), nous avons étudié la réorganisation de la représentation cérébrale du sens des mots. Chez les aveugles, l'accès au sens des mots a le même décours temporel que chez les sujets voyants, mais il recrute le cortex occipital en sus des régions habituelles. Enfin, nous avons observé une variabilité individuelle plus importante chez les aveugles dans l'organisation cérébrale du système sémantique. Nos résultats contribuent ainsi à la compréhension de la réorganisation cérébrale dans la cécité, et plus généralement du rôle de l'expérience perceptive dans le développement.

List of publications

- **Abboud S**, Cohen L. Distinctive expansion of cognitive networks into the visual cortex in the blind. (under revision). Included in Chapter 2
- **Abboud S***, Engemann D*, Cohen L. Semantic coding in the visual cortex of the early blind (in preparation). Included in Chapter 3
- Barttfeld P*, **Abboud S***, Lagercrantz H, Adén U, Padilla N, Edwards AD, Cohen L, Sigman M, Dehaene S & Dehaene-Lambertz G. A lateral-to-mesial organization of human ventral visual cortex at birth. (under revision). Included as Appendix A

Previously conducted research that was published during the PhD:

- **Abboud S**, Maidenbaum S, Dehaene S , Amedi A. A number-form area in the blind. Nat. Commun. 6:6026 doi: 10.1038/ncomms7026 (2015)
- Peer M*, **Abboud S***, Hertz U, Amedi A, Arzy S. Intensity-based masking: a tool to improve functional connectivity results of resting-state fMRI. Hum. Brain Mapp., 37, pp. 2407-2418, doi: 10.1002/hbm.23182 (2016)

Presentations:

- **Abboud S**, Maidenbaum S, Dehaene S, Amedi A. (2015). A number-form area in the blind. *Concepts, Actions, and Objects, Rovereto, Italy.* (talk and poster award)
- **Abboud S**, Maidenbaum S, Dehaene S, Amedi A. (2015). A number-form area in the blind. *16th International Multisensory Research Forum (IMRF), Pisa, Italy.* (talk)
- **Abboud S**, Cohen L. (2016). Modularity in the occipital lobe of the congenitally blind. *Concepts, Actions, and Objects, Rovereto, Italy.*
- **Abboud S**, Cohen L. (2016). Modularity in the visual cortex of the congenitally blind. *Fifth Biennial Conference on Brain Connectivity, Vienna, Austria* (short talk)
- **Abboud S**, Engemann D, Cohen L. (2018) Decoding semantic information in the visual cortex of the early blind. *European Workshop on Cognitive Neuropsychology, Bressanone, Italy.* (short talk)

Abbreviations

ACC	anterior cingulate cortex
AUC	area under the curve
CSF	cerebrospinal fluid
DLPFC	dorsolateral prefrontal cortex
DTI	diffusion tensor imaging
EB	early blind
EEG	electroencephalography
ERP	event-related potential
FC	functional connectivity
FDR	false discovery rate
FEF	frontal eye-fields
fMRI	functional MRI
GLM	general linear-model
hMT+	the human equivalent of monkey middle temporal area
HRF	hemodynamic response function
ICA	independent component analysis
IFG	inferior frontal gyrus
IFS	inferior frontal sulcus
IPS	intraparietal sulcus
LGN	lateral geniculate nucleus
LOC	lateral occipital complex
MEG	magnetoencephalography
MGN	medial geniculate nucleus
MMN	mismatch negativity
MNE	Minimum Norm Estimates
MNI	Montreal Neurological Institute
MOG	middle occipital gyrus
MRI	magnetic resonance imaging
MVPA	multivariate pattern analysis
NFA	number-form area
PET	positron emission tomography
PPA	parahippocampal place area
PPC	posterior cingulate cortex
rCBF	regional cerebral blood flow
ROI	regions of interest
rTMS	repetitive TMS
SFC	superior frontal cortex
SFG	superior frontal gyrus
SMG	supramarginal gyrus
SNARC	spatial numerical association of response codes
SOG	superior occipital gyrus
STG	posterior superior temporal gyrus
STS	superior temporal sulcus

STS	superior temporal sulcus
TMS	transcranial magnetic stimulation
V1	primary visual cortex
V2	secondary visual cortex
VOTC	ventral occipital-temporal cortex
VWFA	visual word-form area

1. Introduction

The human neocortex consists of regions that specialize in processing different types of information ranging from low-level sensory input to high-level meta-cognition. An ongoing effort is devoted to understanding how this specialization develops. In the case of primary sensory cortices, early studies used invasive experimental manipulations in animal models to study this specialization. For example, the pioneering work by Wiesel and Hubel (1963) demonstrated the elimination of responses to light in the cat visual cortex due to prolonged eye-lid closing shortly after birth. More invasively, bilateral retinal ablations of primate fetuses in utero lead to an unusual cytoarchitectonic organization of primary visual cortex (Rakic et al. 1991; Dehay et al. 1996). Pushing the system even further, Sur et al. (1988) induced retinal projections into auditory cortex through the medial geniculate nucleus (MGN). They were later able to record visual responses from single units in auditory cortex of operated ferrets, a finding that provoked the question: What is intrinsically visual about the visual cortex?

Furthermore, auditory responses in visual areas of the cat were also possible to induce without surgical manipulations. By depriving cats from vision for several years shortly after birth, Rauschecker et al. (1993) demonstrated that neurons in the anterior ectosylvian visual area responded strongly to auditory stimuli. Those neurons had purely visual responses in normal cats but are thought to have underwent a compensatory plastic process, often termed “crossmodal plasticity”, resulting in the recruitment of the input-deprived cortex by the remaining intact senses (Rauschecker 1995). An analogous effect was also observed in the auditory cortex of cats deafened from birth where most neurons in the anterior auditory field were activated by somatosensory stimulation (Meredith and Lomber 2011).

In humans, where experimental manipulations are not possible, individuals with congenital peripheral sensory deprivation enable studying cortical specialization. Having no sensory input at birth, in an

otherwise intact system, allows probing the role of experience on the fate of cortical regions. This dissertation focuses on the effects of the lack of visual input from the retina on the organization and functions of the human visual cortex.

I begin this chapter with the definition of blindness that we adopted and the behavioral consequences of being born blind. Then, I review findings on the recruitment of the visual cortex in the blind by a spectrum of functions ranging from the perceptual to the cognitive. I also review anatomical and functional connectivity alterations caused by blindness. Throughout this review, I refer to theories put forward to explain the observed functional reorganization of the occipital cortex. Finally, I conclude by introducing the studies included in this dissertation, which, first, target the activation of the visual cortex by high-order cognitive functions in the blind and relate those activations to its functional connectivity to the rest of the brain. Second, test the proposal that innate connectivity underlies this functional activation, and third, investigate whether the visual cortex in the blind codes semantic information.

1.1. Blindness – definition

The global blind population amounts to just under 40 million individuals with varying etiology and age of onset (World Health Organization 1992). The World Health Organization defines blindness as a corrected visual acuity in the better eye of less than 3/60 or a central visual field of less than 10°. However, to investigate the effect of *the lack of visual input from the retina to the cortex*, one must adapt a stricter definition of blindness. Put simply, individuals should be completely blind, at birth, and with no cortical deficits. More formally, we use the etiological classification of childhood blindness proposed by Foster and Gilbert (1992):

1. factors which act at the time of conception, e.g., genetic and chromosomal abnormalities
2. factors operating during the intra-uterine period, e.g., infections (rubella, toxoplasmosis), toxins (alcohol, quinine)
3. factors operating at the time of birth or during the post-natal period, e.g., cerebral hypoxia, retinopathy of prematurity and ophthalmia neonatum
4. factors operating in childhood, e.g., vitamin A deficiency, trauma

Using the above classification, this thesis adopts the following definition of blindness:

a) part of classes 1, 2 or 3
b) primary cause is anterior to optic chiasma
c) no residual vision or light perception

Fulfilling those three criteria is thought to establish, as much as possible, a common developmental state in the visual cortex across individuals. Individuals who abide to this definition constitute a small part of the global blind population and their exact number is largely unknown and difficult to estimate. The definition of blindness and naming conventions vary throughout the scientific literature. For example, most studies in the blind included individuals with faint light perception and no form perception. However, to date, investigations targeting the influence of faint light perception are scarce (cf. Wong et al. 2011). Therefore, as a precaution and in order to minimize between-subject variation, this work included only volunteers that declared having no light perception. Concerning terminology, I will opt for using the term early blindness due to the inclusion of individuals who lost their sight during the post-natal period (usually up to 6 weeks from birth). However, some authors have used the term congenital blindness when referring to similar individuals (e.g. Reich et al. 2011) and early blindness when including individuals that lost their sight as late as the age of 5 (e.g. Burton et al. 2006). Throughout this dissertation, the term blind will be used as a shorthand for early blind and etiology will be explicitly stated when referring to a different group (e.g. late blind). Finally, the somewhat figurative "blind visual cortex" will at times serve as a substitute for the longer "visual cortex of the blind".

1.2. Behavioral consequences of blindness

Throughout history, philosophers - and later scientists - were intrigued by blindness and its consequences on human behavior. The blind had inspired reflections on the mental representation of the world. Most famously, the correspondence between John Locke and William Molyneux, the Irish philosopher, which later became known as Molyneux's problem: Imagine an individual that was born blind and learned the shapes cube and globe using tactile input. If this person were able to see one day, would they be able to distinguish the cube from the globe only based on vision? Locke and Molyneux seemed to agree that the answer is no, implying that representations depend on sensory modality (Degenaar 1996). In a different account some centuries beforehand, Ibn Tufayl, the Arab Andalusian polymath, postulates a contradicting view. Imagine a blind person, "with good capacity […] and solid judgment", if able to see one day "would find every thing to be exactly agreeable to those notions which he had before; and that colours were such as he had before conceived them to be, by those descriptions he had received". The only difference, hence, between blindness and sight would be "clearness and extreme delight" (Ockley 1708 in a translation of Ibn Tufayl). Thus, implying a more abstract underlying representation.

More functionally, Diderot, in his “Lettre sur les aveugles” (letter on blindness; 1749), stated confidently that the congenitally blind develop supernormal powers of touch and hearing, which substitute for their loss of vision (Morgan 1999). Over two centuries later, in 2007, the Belgian police recruited blind individuals as detectives because of their skill in segregating speech in recordings with low signal-to-noise ratio (Hötting and Röder 2009).

Notwithstanding the mythical tone of the previous lines, blindness does require a drastic behavioral adaptation. Not able to benefit from visual cues, the blind revert to using tactile, auditory and olfactory strategies to negotiate the world. It is therefore tempting to presume that vision is compensated for by extra computational power to the intact senses. In the next section, I will summarize findings regarding the behavioral differences between the sighted and the early blind.

1.2.1. Perception

1.2.1.1. Tactile

Comparing the tactile perceptual abilities between the early blind and the sighted showed both the superiority of the blind and the superiority of the sighted but also similarity between the groups. Even when considering the same tactile ability, e.g., grating orientation detection with the fingertips, some results favor the blind (Van Boven et al. 2000; Goldreich and Kanics 2003; Wong et al. 2011) while others find no difference between the blind and the sighted (Grant et al. 2000; Alary et al. 2009). Otherwise, the blind were found similar to the sighted in vibrotactile frequency detection (Grant et al. 2000), surface texture discrimination acuity (Heller 1989; Grant et al. 2000), object shape matching (in children Withagen et al. 2012), dot-pattern discrimination (Stilla et al. 2008), and bar length discrimination (Stevens et al. 1996). Better performance in the blind was demonstrated in real-world texture discrimination (Gurtubay-Antolin and Rodríguez-Fornells 2017), angle size discrimination with the arm out-stretched (but not when the elbow was restrained; Alary et al. 2008), and dot-pattern discrimination (this advantage disappeared after practice; Grant et al. 2000). Inconsistency in the results across tasks motivated looking into the role of perceptual learning, which could potentially underlie some of the observed variability. Wong and colleagues (2011) probed the role of experience in enhanced tactile abilities by comparing the tactile acuity of the blind to that of the sighted on both fingertips and lips. They reasoned that finding a difference on the fingertips but not on the lips favors the hypothesis that hyper-acuity in the blind is due to experience and not merely due to sensory deprivation. Indeed, they showed that while acuity on the lips was similar in both groups, fingers have a higher tactile acuity in the blind. Moreover, the acuity in the fingers used for Braille-reading was correlated with weekly Braille-reading time. Hence, providing evidence of an experience-dependent mechanism, at least for tactile

acuity in grating orientation detection (Wong et al. 2011). Notwithstanding, the joint influence of sensory deprivation and experience-dependent mechanisms on tactile perception in the blind is far from being fully understood (Sathian and Stilla 2010).

1.2.1.2. Auditory

In general, the blind were found equivalent to the sighted in absolute auditory detection thresholds and reaction time to sounds (Collignon et al. 2006; Cornell Kärnekull et al. 2016). When considering spectral and temporal processing abilities, the early blind show an advantage, when compared to the sighted and the late blind, in pitch discrimination (Gougoux et al. 2004; Rokem and Ahissar 2009; Lerens and Renier 2014) and pitch-timbre categorization (even when controlling for musical training; Wan et al. 2010). Also, absolute pitch was found to be more prevalent in early blind musicians (Hamilton et al. 2004). The blind also show a better ability to organize sounds sequentially, supporting an enhanced processing of incoming acoustic information (Boroujeni et al. 2017). In this line, Stevens et al. (2005) used auditory backwards masking to show that an early arrival of a post-stimulus mask impaired performance only in the sighted, providing evidence for an advantage in auditory perceptual consolidation in the blind. When considering verbal input, the blind made less errors during dichotic listening to phonemes (Hugdahl et al. 2004). They also showed an advantage in speech perception with background noise (Niemeyer and Starlinger 1981; Muchnik et al. 1991; Rokem and Ahissar 2009) and in ultra-fast speech comprehension (Gordon-Salant and Friedman 2011; Dietrich et al. 2013).

When considering spatial tasks such as sound-source localization, the blind perform similarly to the sighted when the source is in the horizontal axis (Lessard et al. 1998; Röder et al. 1999; Zwiers et al. 2001a; cf. Macé et al. 2012). They show an advantage, however, when the sources are in the peripheral auditory space (Röder et al. 1999). In addition, a study by Lessard et al. (1998) found that half of the tested blind subjects were able to accurately locate sound-sources monaurally (with one ear blocked) where the sighted presented a systematic bias towards the open ear (Morgan 1999; Van Wanrooij and Van Opstal 2004). This supra-normal ability was later attributed to the more effective use of spectral cues by the blind (Doucet et al. 2005; Voss et al. 2011). In the vertical axis, on the other hand, the blind often perform worse than the sighted (Lewald 2002), especially so under low-SNR conditions (Zwiers et al. 2001b). In a recent study, Voss et al. (2015) showed that the highest performing subjects in monaural localization in the horizontal space are the worst in the vertical space and vice-versa. Thus, providing evidence to support a trade-off in learned perceptual expertise.

When judging distance from sound-source, the blind show an advantage over the sighted for tasks that rely on relative auditory distance information (Voss et al. 2004; Kolarik et al. 2013) but not when relying

on absolute auditory distance information (Wanet and Veraart 1985; in adolescents Lai and Chen 2006; in a mixed group of early and late blind Macé et al. 2012; Kolarik et al. 2013). This difference is thought to depend on the fact that the blind possess an internally intact distance representation that is not well-calibrated to the environment due to the absence of vision (Kolarik et al. 2016). Moreover, a major deficit was demonstrated in the blind by using a complex task where subjects had to judge whether the second in a series of three sounds is spatially closer to the first or the third, highlighting further the importance of vision in the calibration of auditory representations (Gori et al. 2014; present also in children Vercillo et al. 2016).

Hence, the emerging picture is that while some auditory functions are enhanced following vision loss, others are impaired. This might reflect the balance between adaptation for blindness and the role of vision in calibrating the auditory space (King 2015).

1.2.1.3. Olfactory & Gustatory

Higher olfactory performance has been observed in the blind when performing a task of free odor identification (Murphy and Cain 1986; Rosenbluth et al. 2000; Wakefield et al. 2004 in children; cf. Cuevas et al. 2010; Rombaux et al. 2010). This advantage was not present, however, in multiple-choice odor identification (Smith et al. 1993; Rosenbluth et al. 2000; Cuevas et al. 2009, 2010; Beaulieu-Lefebvre et al. 2011; Çomoğlu et al. 2015). An advantage in olfactory sensitivity thresholds was present in some studies (Cuevas et al. 2010; Beaulieu-Lefebvre et al. 2011; Çomoğlu et al. 2015) but not in others (Murphy and Cain 1986; Smith et al. 1993; Rosenbluth et al. 2000; Wakefield et al. 2004 in children). Similarly, some studies showed an advantage for the blind in odor discrimination (Cuevas et al. 2009, 2010; Rombaux et al. 2010; Çomoğlu et al. 2015) while others showed similarity to the sighted (Smith et al. 1993; Beaulieu-Lefebvre et al. 2011). Interestingly, a group of highly trained sighted individuals outperformed both the blind and their sighted controls in odor discrimination (Smith et al. 1993). This suggests that training might be more influential than blindness per se when considering olfactory abilities. Therefore, the overtraining in the blind might confound the interpretation of their superior abilities. Teasing apart the roles played by blindness and training in olfactory abilities would be a useful next step that could help reconcile the reviewed inconsistent findings.

Much less studied is gustatory sensitivity. Recent evidence points to generally worse performance in the blind when compared to the sighted (Gagnon et al. 2013). However, past studies also showed abilities that are equivalent to the sighted (Smith et al. 1993).

1.2.1.4. Beyond the traditional senses

Beyond the scope of this dissertation is the impact of blindness on navigation and the development of echolocation skills by some blind individuals. Echo-locating individuals produce mouth clicks, for example, and listen to their echo in order to 'reveal' their surroundings. Some individuals are even able to determine information such as the shape and material of objects. Evidence suggests that even when controlling for training, the blind are able to achieve better performance in echolocation tasks (Kolarik et al. 2014). For navigation, the reader is referred to a literature review and discussion by Schinazi et al. (2016).

1.2.2. High-order cognition

Perceptual differences between blind and sighted individuals might be expected due to the different ways the two groups experience the world. How would, however, blindness influence cognitive functions?

1.2.2.1. Numerical skills and language

In numerical cognition, the blind made fewer errors while solving certain basic arithmetic operations, e.g., 9x8 (Dormal, Crollen, et al. 2016) but were not found different from the sighted when solving problems requiring more calculations, e.g., 2 peaches cost 17 cents, how much would a dozen cost? (Rokem and Ahissar 2009). They also performed better than the sighted at numerical estimation (Castronovo and Seron 2007a; Castronovo and Delvenne 2013). Also, the blind demonstrated both the classical numerical distance effect (Szűcs and Csépe 2005) and the SNARC (spatial numerical association of response codes) effect (Castronovo and Seron 2007b) indicating that certain numerical processes do not depend on visual experience.

For language skills, the blind presented higher performance than the sighted in a task of verbal fluency, e.g., produce the largest number of words that start with a certain phoneme, (Occelli et al. 2017).

1.2.2.2. Executive functions

Classical measures of executive abilities use span tasks where subjects are asked to recall a list of items in order. When measuring recalling span scores, the emerging picture is not very clear. On the one hand, simple digit-, word- and pseudo-word- span scores are mostly found to be higher in the blind (Rokem and Ahissar 2009; Crollen et al. 2011; in children Withagen et al. 2013; Dormal, Crollen, et al. 2016). On the other hand, when adding computational complexity, we find heterogeneous results. In repeating the digits backwards, for example, some authors found that the blind were better than their sighted counterparts (in children Withagen et al. 2013; in adults Occelli et al. 2017) while others did not (Rokem and Ahissar 2009; Castronovo and Delvenne 2013). Similarly, using a task that requires recalling the last word of sentences, some studies showed an advantage to the blind (in children Withagen et al. 2013)

while others failed to do so (in children Crollen et al. 2011). In addition, Rokem et al. (2009) found that when controlling for perceptual input the blind lose their advantage in verbal memory span for pseudo-words. Thus suggesting that enhanced stimulus encoding is responsible for the enlarged span as opposed to better executive processing. In line with this suggestion are studies that failed to find an advantage for the blind in tasks of pitch working-memory (Wan et al. 2010), n-back for consonants (Pigeon and Marin-Lamellet 2015) and n-back with Braille letters for the blind and written letters for the sighted (Bliss et al. 2004).

1.2.2.3. Memory

When considering memory capacities, the blind were found better than their sighted counterparts at judging if words were part of previously heard sentences (Röder et al. 2001). They were also found to retain more words from a list of pre-learned abstract words (Amedi et al. 2003; Raz et al. 2005; Occelli et al. 2017). Also, they performed better when recalling words according to their serial position of presentation (Raz et al. 2007) and showed reduced false memory effects (Pasqualotto et al. 2013). Better memory performance was also observed for environmental sounds (e.g. motorcycle) when comparing to the sighted but not to the late blind (Röder and Rösler 2003; Cornell Kärnekull et al. 2016).

1.2.2.4. Attention

The blind showed shorter response times in several attentional tasks (e.g. selective attention) using both auditory and tactile stimuli (Collignon et al. 2006; Pigeon and Marin-Lamellet 2015). However, the latter study showed that performance in selective, sustained and divided attention did not differ from the late blind when using consonants as targets and one-digit numbers as distractors. Also, no advantage to the favor of the blind was observed in task-switching costs (Pigeon and Marin-Lamellet 2015). Using dichotic listening, Hugdahl et al. (2004) provided evidence for an enhanced tuning of attention in the blind. Subjects were able to focus their attention to one ear inhibiting input from the other in order to identify auditory syllables. Furthermore, the blind presented an equally distributed attention across space and, unlike the sighted, did not favor the frontal part of space (Lerens and Renier 2014).

To summarize, blind individuals do show an advantage when compared to the sighted. However, this advantage is neither general nor extensive. It is fairly restricted and it depends on task specificities, sensory modality and expertise. Moreover, under specific circumstances, the blind can also present a deficit in performance. Therefore, the presumption that blind individuals compensate for their lack of vision with more powerful auditory, tactile, olfactory and gustatory abilities should be carefully substantiated and not taken for granted.

Considering studies where a behavioral enhancement was observed in the blind, one cannot but pose the following question: Are the observed effects strictly due to visual deprivation? In this regard, two competing hypotheses are to be considered: 1) The visual deprivation hypothesis: the absence of vision by itself enhances performance; 2) The experience hypothesis: training on a specific task results in better performance. Wong et al. (2011), mentioned earlier, found results that favor hypothesis number 2 because the enhanced acuity was related to the level of expertise on the fingertips and was not at all found on the lips. In a study targeting the effect of visual deprivation in normal adult subjects, Merabet et al. (2008) implemented a 5-day tactile training program while blindfolding half of the subjects for the whole duration of the experiment. They demonstrated that, at the last day of the experiment, tactile acuity measures improved for both the blindfolded and non-blindfolded subjects. However, the blindfolded group made less errors in a Braille letter discrimination task. Hence, demonstrating in normal subjects, that both visual deprivation and training play a role in influencing tactile performance. Therefore, in blind individuals, several mechanisms are possibly at play including deprivation age, training and the specific functionality at hand. An exploration of the interaction between those factors is beyond the scope of this dissertation.

1.3. Functional recruitment of the visual cortex

In contrast to the at times inconsistent account of behavioral differences between the blind and the sighted, looking at the brain unveils substantial differences resulting from the lack of vision. At the center of attention is the visual cortex that occupies the occipital lobe extending from the striate and extrastriate cortices both ventrally and dorsally towards the temporal and parietal lobes. Early work by Wanet-Defalque et al. (1988) studying the anatomy of the visual cortex in the blind found that it is qualitatively undistinguishable from the visual cortex of the sighted when imaged using magnetic resonance imaging (MRI). In addition, the authors reported that the regional cerebral metabolic rate for glucose, measured using positron emission tomography (PET), is higher in the blind when compared to blindfolded sighted controls. They concluded that the visual cortex in the blind is indeed functioning and

raised questions concerning its functions. The following sections summarize the efforts dedicated to delineating those functions.

1.4. Early evidence for a functional role

In one of the first attempts to probe the functions of the visual cortex in the blind, Uhl et al. (1991) compared Braille reading to passing the finger over random dot-patterns. The authors found greater occipital negativity in the blind using scalp-recorded event-related slow negative DC potential shifts. Using a similar task, Uhl et al. (1993) showed higher regional cerebral blood flow (rCBF) indices in the blind when compared to the sighted, but failed to show any differences between the two tasks. It was a few years later that Sadato et al. (1996) confirmed the existence of a task-dependent differential response in the visual cortex of the blind. Braille reading resulted in stronger rCBF than sweeping over a surface homogenously covered with Braille dots. Although not tested for statistically, they also showed that tactile tasks such as judging the width of two grooves also activate the visual cortex of the blind but to a lesser extent. This activation was regarded as a manifestation of crossmodal plasticity in vision-deprived humans (Sadato et al. 1996). Reinforcing the functional relevance of the visual cortex in the blind was a study by Cohen et al. (1997) using transcranial magnetic stimulation (TMS). The authors were able to impair the identification of both Braille and embossed Roman letters in the blind when stimulating the mid-occipital cortex but not when stimulating the somatosensory cortex. Hence, establishing the causal role of the visual cortex in letter identification when performed by early blind individuals. TMS to the occipital cortex was also shown to induce sensations on the fingertips of blind Braille readers, in contrast to the sensations of light produced in the sighted (Ptito, Fumal, et al. 2008). Finally, a case of alexia for Braille following an ischemic occipital stroke in an early blind woman provided even more compelling evidence that the visual cortex is essential to Braille reading (Hamilton et al. 2000).

1.5. Specialized functional recruitment

Previously mentioned studies concentrated on the question whether the blind visual cortex is needed for Braille reading. However, Braille reading involves sensory, motor, associative, and executive processes in addition to language functions. Every one of those single functions could, in principle, underlie the Braille-related activation of the visual cortex. Thus, to better understand visual activation in the blind, individual, more circumscribed, processes and functions were studied. What follows is a review of the literature where each section will focus, as much as possible, on specific functions starting

from low-level perceptual processing going up the cognitive hierarchy to the execution of high-order functions.

1.5.1. Somatosensory processing

Gizewski et al. (2003) showed that neither median nerve stimulation nor finger tapping activated the visual cortex in the blind suggesting that it is not mere sensory stimulation that is responsible for the visual activation. Supporting this suggestion is the finding that TMS delivered to primary visual cortex (V1) while identifying Braille letters impaired letter identification and not detection in contrast to stimulating primary somatosensory cortex that impaired detection (Hamilton and Pascual-Leone 1998). These results are in line with studies that found no somatosensory processing in the visual cortex when no task was involved (e.g., Sadato et al. 1996; Beisteiner et al. 2015; Pishnamazi et al. 2016). On the other hand, when subjects are asked to perform a task on the perceived stimuli, a different picture emerges. The visual cortex of the blind is recruited during a variety of somatosensory tasks. For example, Rösler et al. (1993) found a pronounced occipital activity in the blind when encoding tactile shapes for a consecutive mental rotation task. Among other examples are the detection of the orientation of gratings applied to the fingertip (Lewis et al. 2010), the orientation of T shapes stimulated on the tongue using an electrode array (Ptito et al. 2005), and the amplitude change of vibro-tactile stimuli (Burton et al. 2010). The visual cortex of the blind is also recruited when performing same/different tasks on the frequency of vibro-tactile stimuli (Burton et al. 2004, 2010) as well as on more elaborate stimuli such as shoes, plastic bottles and masks of faces (Pietrini et al. 2004) and plastic animals that could either be mammals or not (Lewis et al. 2010).

All the above mentioned studies, however, used the non-specific task > rest contrast which resulted in an extensive activation in the visual cortex. This use is not optimal because such contrasts may include many cognitive processes (e.g. executive) that can render the interpretation of activations very difficult. To overcome this problem, Stilla et al. (2008) designed a task of spatial dot-pattern discrimination with a stricter control condition. In the main spatial condition, subjects had to judge if the middle dot in a series of 3 dots is offset to the right or to the left. In the control, temporal, condition, subjects were stimulated for 0.7 and 1.3 s and had to judge if the stimulation duration was short or long (Figure 1.1).

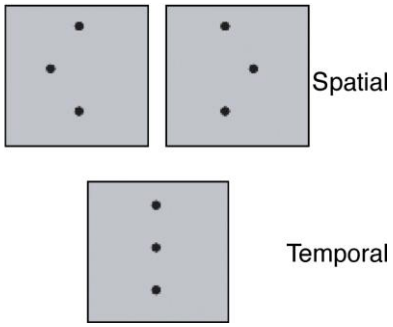


Figure 1.1 – Tactile task conditions used by Stilla et al. (2008). Dot configurations in the: spatial condition where subjects had to judge if the middle dot is displaced to the left or to the right; and temporal condition where subjects had to judge the duration of stimulation of all 3 dots.

When comparing the main condition to the control condition, they found activations in the left lingual gyrus and right collateral sulcus in addition to bilateral dorsal activations in the parieto-occipital fissure (Figure 1.2a; Stilla et al. 2008).

Also using a controlled design, Voss et al. (2016) showed a right-lateralized activation in the superior and middle occipital gyri (SOG & MOG) that is modulated by task difficulty of tactile angle-size identification (Figure 1.2b). Additionally, a right-lateralized cluster in the precuneus, sensitive to the symmetry of tactile Braille-like dot patterns, was found when comparing the blind to the sighted (Bauer et al. 2015).

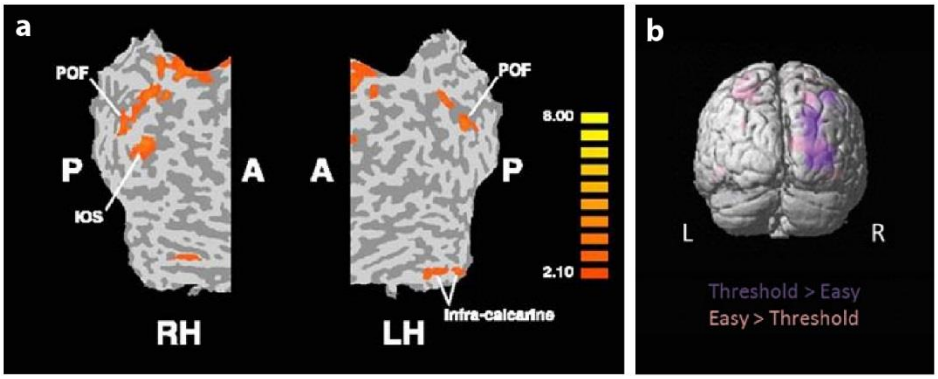


Figure 1.2 – Brain activation during controlled tactile tasks. a | Activation in the spatial > temporal conditions overlaid on a flattened brain. POF=parieto-occipital fissure, IOS=intra-occipital sulcus. Adapted from Stilla et al. (2008). **b** | Comparing difficult to easy angle-size identification in the blind. Adapted from Voss et al. (2016).

1.5.2. Auditory processing

In contrast to somatosensory processing, under no or low attentional demands, certain studies found that auditory stimulation activated the visual cortex in the blind (e.g. Arnaud et al. 2013; Watkins et al. 2013 in anophthalmic subjects; Pishnamazi et al. 2016) while others did not (Kujala et al. 1995; e.g. Weeks et al. 2000; Stevens and Weaver 2009). Such differences may depend on technical factors such as scanner noise and experimental factors such as the nature of the stimuli and the instructions given to the subjects. Indeed, with the exception of a study in anophthalmic subjects that reported an activation

in hMT+/V5 while subjects passively listened to tone trains of 1 s (Watkins et al. 2013), studies not finding an activation for passive auditory stimulation often used functional MRI (fMRI) sampling techniques where the scanner noise does not coincide with the stimuli (e.g. Stevens and Weaver 2009).

When performing sound-source localization, early electrophysiological studies generally showed more posterior scalp distributions in the blind compared to the sighted (Kujala et al. 1992; Leclerc et al. 2000). Using imaging, higher rCBF was measured in the right visual cortex of the blind (Weeks et al. 2000). More specifically, higher performance for peripheral sources in the blind was correlated with a more spatially tuned and more posteriorly distributed N1 response (Röder et al. 1999). Moreover, studies have shown that the blind could be split into two groups: 1) individuals who perform better than the sighted on monaural sound-source localization; 2) individuals who perform like the sighted (e.g. Lessard et al. 1998). Only subjects that performed well monaurally were found to activate the right cuneus and lingual gyrus during both monaural (Gougoux et al. 2005) and binaural sound-source localization (Voss et al. 2008). Moreover, in those high performing blind subjects a correlation between performance and change in CBF was found in right striate cortex in addition to the lingual and superior occipital gyri (Gougoux et al. 2005). This finding established a link between superior performance in the blind and activity in their visual cortex. In support of that, TMS delivered to the right dorsal occipital cortex 50msec after stimulus onset successfully disrupted spatial sound processing in the blind. However, it should be noted that a disruption effect was also observed in the sighted, but possibly due to different mechanisms (Collignon et al. 2009).

Using a well-controlled design comparing a task of sound-source localization to pitch discrimination, Collignon et al. (2011) showed that, only in the blind, the localization task activated the right cuneus, middle occipital and lingual gyri more than the pitch task. They found no regions favoring the pitch discrimination task over the localization task that are specific to the blind. Similar results in the middle occipital gyrus (MOG) were found by Renier at al. (2010) that used a one-back design of sound-source location and frequency judgment.

Surprisingly, activation for human generated voices when compared to environmental sounds or object generated sounds does not recruit the visual cortex in the blind (Gougoux et al. 2009; Dormal et al. 2018). It does, however, result in a stronger activation in the posterior superior temporal gyrus (pSTG) that is correlated with speaker identification performance (Gougoux et al. 2009). However, a small congruency effect in the right anterior fusiform was found using a priming paradigm where speaker identity was either congruent or incongruent between two consecutive non-word stimuli (e.g. ‘dede’; Hölig et al. 2014). This finding is in agreement with electroencephalography (EEG) data showing a

speaker-related congruency effect during the N100 response with a scalp distribution that is more posterior in the blind than in the sighted (Föcker et al. 2012).

1.5.3. Modality-independent perceptual processing

The intact auditory and tactile sensory modalities were shown to elicit activity in the visual cortex of the blind. However, several activated regions were found to be sensitive to more than one sensory modality. Using a one-back task on the location and frequency of tactile and auditory stimuli, Renier et al. (2010) demonstrated that the activation in the middle occipital gyrus (MOG) of the blind is modality independent. Namely, this region was found significant in the contrast of localization minus frequency detection no matter if the stimuli were auditory or tactile. Moreover, MOG is a part of the visual dorsal "where" stream that is involved in visuospatial computations in normal individuals (Haxby et al. 1991). Such instances lead authors to suggest that crossmodal plasticity is constrained by the predisposed functions of cortical regions (Figure 1.3a; e.g. Renier et al. 2010; Collignon et al. 2011). Hence, the MOG in the blind will be recruited for spatial computations since it implements visuospatial computations in the sighted. This suggestion is supported by evidence of overlapping activations between visual tasks in the sighted and equivalent auditory and tactile tasks in the blind. Most investigated in this regard, perhaps, is the selectivity for motion in hMT+, the human equivalent of monkey middle temporal area (Braddick et al. 2001). In the blind, using motion sounds and moving tactile Braille-like patterns, this region has been shown to selectively respond to auditory and tactile motion and to code for its direction (Figure 1.3b; e.g. Ricciardi et al. 2007; Jiang et al. 2014; Dormal, Rezk, et al. 2016). Moreover, TMS delivered to hMT+ disrupted the discrimination of motion direction for a single moving tactile point on the fingertip, establishing its causal role in tactile motion processing (Amemiya et al. 2017). Similarly, in the blind and in the sighted, tactile shape identification was shown to activate a region in LOC thought to be selective for visual object shape (Malach et al. 1995; Prather et al. 2004; Amedi et al. 2010). In addition, it has been shown that Braille reading by the blind also activates the visual word-form area (VWFA), normally processing visual orthography and thus active when reading (Figure 1.3c; Cohen 2002; Reich et al. 2011).

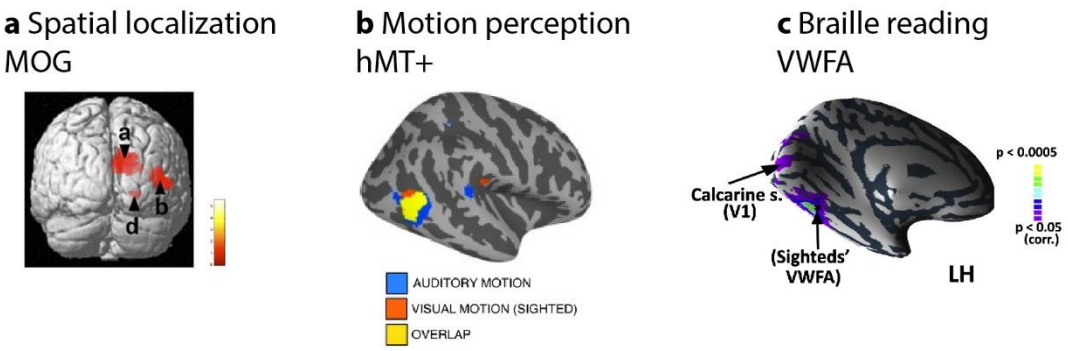


Figure 1.3 – Task overlap between the sighted and the blind. a | Activation in the MOG where the blind were stronger than the sighted in a contrast between a sound-source localization and pitch detection tasks. Adapted from Collignon et al. (2011). **b** | Activation for motion perception in hMT+ of the sighted using visual stimuli (orange) and the blind using auditory stimuli (blue) and their overlap (yellow). Adapted from Dormal, Rezk et al. (2016). **c** | Activation during covert Braille reading (words compared to six-dot Braille characters) that peaked in close vicinity to the sighted VWFA (marked with an arrow). Adapted from Reich et al. (2011).

This line of evidence could be accounted for by the "metamodal organization of the brain" theory, proposed by Pascual-Leone and Hamilton (2001). At its core, this theory postulates that the brain consists of operators that execute a given function regardless of sensory input modality. This is not to say, however, that certain computations do not have a predilection for specific sensory input. Consequently, unisensory cortical regions only give the impression of being sensory-specific by selectively reinforcing certain sensory inputs due to this predilection. In the face of visual deprivation, however, visual cortex will implement its intrinsic computations by using and reinforcing its auditory and tactile inputs (Pascual-Leone and Hamilton 2001).

Approaching the vision-deprived brain from a metamodal perspective was facilitated by sensory-substitution techniques that transform information usually perceivable by one sense into information perceivable by another (Bach-y-Rita et al. 1969). For example, vision-to-audition sensory-substitution translates visual information (e.g. geometric shapes) into auditory information (e.g. pure tones). Crucially, such transformations should preserve the structure of the information. For example, in the case of vision-to-audition sensory-substitution, geometric shape information should be extractable from the produced sounds. This lies in contrast to mappings that are based on abstract associations, e.g., a drum hit represents a triangle.

Using visual shapes substituted into auditory stimuli with an object identification task, Amedi et al. (2007) showed that LOC is activated in the sighted and in the blind with a contrast of object shape versus object typical sound. Moreover, using auditory stimuli of shapes in different spatial locations, Striem-Amit et al. (2012) showed that the segregation between the ventral "what" and dorsal "where"

streams persists also in the blind. When subjects were asked to identify the shape, they activated the ventral stream extensively, whereas they activated the precuneus in the dorsal stream when asked to identify the location of the stimulus. Also using an identification task of auditory renderings in the blind, Striem-Amit et al. (2012) showed that Hebrew letters compared to stimuli from other visual categories selectively activated the VWFA. In addition, we previously showed that, in the blind, the identification of Roman numerals compared with Latin letters activated the number-form area (NFA) residing in the inferior temporal gyrus and thought to be sensitive for symbolic representations of quantity in the sighted (Shum et al. 2013; Abboud et al. 2015). Finally, using visual shapes substituted into tactile stimuli on the tongue, Matteau et al. (2010) showed that hMT+ is activated when comparing moving to static stimulated dots.

This sample represents a larger family of studies that argue for task-preserving plasticity in the visual cortex of the blind. However, the exact nature of the computation executed in those regions remains unclear and is subject for debate. For example, LOC was also activated by the typical sound of objects when compared to human voice, a finding that puts into question its special role as a shape processor (Dormal et al. 2018). Moreover, when considering the VWFA, one finds conflicting evidence. On the one hand, this region is involved in Braille reading in the blind, but on the other hand, as will be presented below, it is also engaged in language comprehension and is sensitive to the grammatical structure of heard sentences (Kim et al. 2017). This lead authors to suggest that visual regions execute different computations in blind and sighted individuals even when appearing to be sensitive to similar features such as motion or reading (Bedny 2017). More on this suggestion will follow in the general discussion of this dissertation.

1.5.4. Higher-order processing

Climbing up the processing hierarchy one step further, some studies suggested that organizational principles governing the ventral occipital-temporal cortex (VOTC) are partly preserved in the blind. For example, the gross medial-to-lateral bias by conceptual domain with medial preference for manmade artifacts and lateral preference to animals has been shown to persist in the blind (Mahon et al. 2009; cf. He et al. 2013). Also, some regions belonging to the category-selective mosaic in VOTC (Grill-Spector and Weiner 2014) show similar category preference in the blind. For example, preference for images of tools usually residing in the lateral occipital-temporal cortex overlapped with activation for tools in the blind during an auditory size-judgment task on heard tool names (Peelen et al. 2013). Similarly, body images encoded using sounds were used to show selectivity for bodies in the right extrastriate body area of the blind (Striem-Amit and Amedi 2014). Those results argue in favor of VOTC's innate disposition to process

information from a specific domain independently of sensory modality (Mahon and Caramazza 2011). In this regard, a study by Wang et al. (2015) had demonstrated that the activation profile in the anterior parts of VOTC for 16 semantic categories is correlated across the blind and the sighted (Figure 1.4a). Finally, in the same line of evidence, van den Hurk et al. (2017) showed that the selectivity mosaic for faces, objects and scenes is similar for audio clips in the blind and short movie clips in the sighted (Figure 1.4b). For example, in the scene category the movie clip depicted breaking waves on a beach while the audio clip contained the sound of waves breaking on the beach. Subjects performed a one-back categorical dissimilarity judgment for both presentation modalities. In addition to showing a similar selectivity mosaic, the authors also demonstrated that training a classifier to distinguish category pairs using data from the VOTC in the blind allowed generalization to VOTC data in the sighted that performed the task visually (van den Hurk et al. 2017). This result reinforces the above reviewed findings in that coding in the VOTC is somewhat abstract and therefore develops independently of visual input to the system.

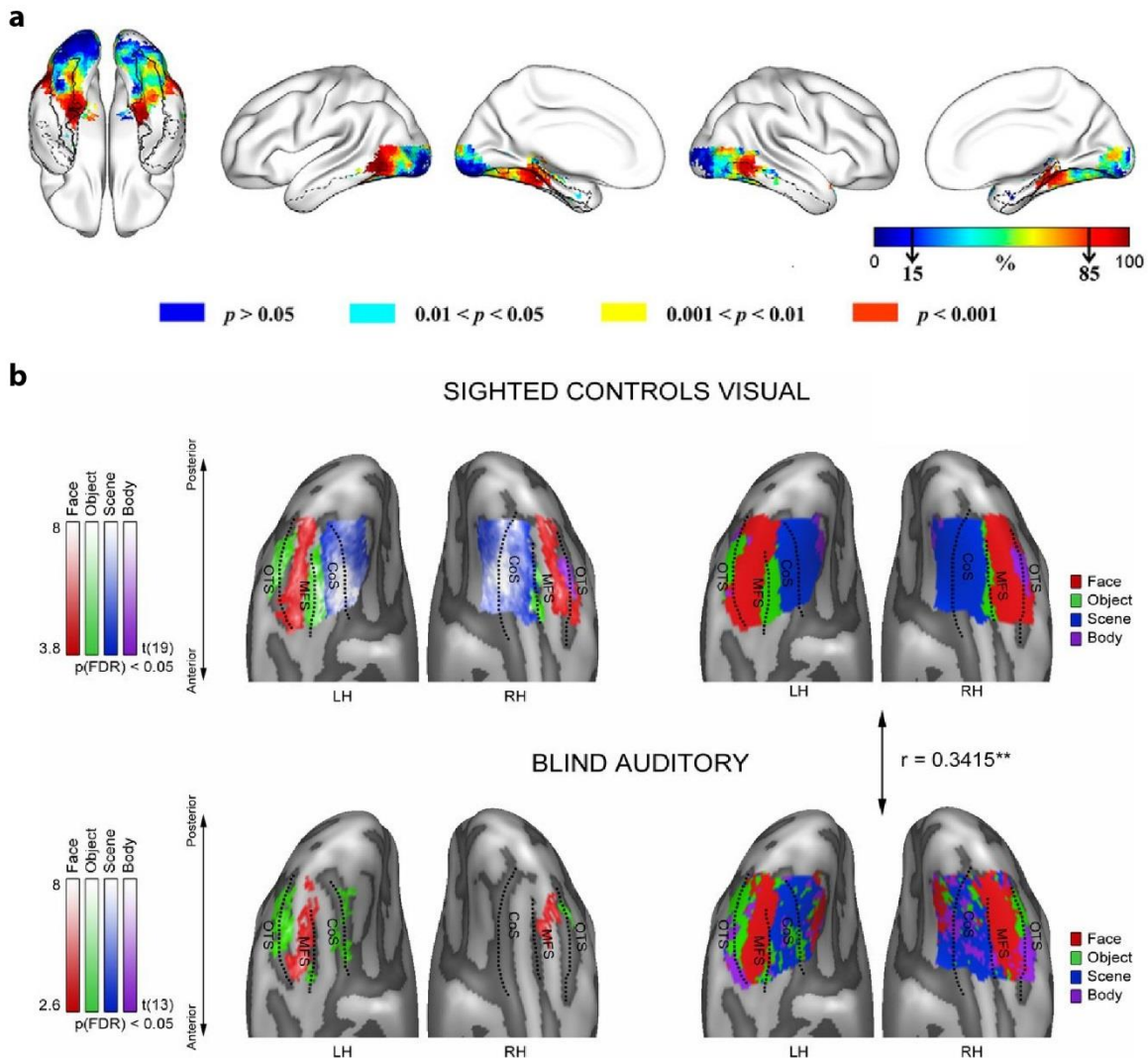


Figure 1.4 – Modality-independent category selectivity in ventral occipitotemporal cortex. a | Correlation between blind and sighted subjects listening to auditory stimuli across 16 semantic categories auditory (percentile rank map). Color bar represents the percentile rank value. Warmer colors represent greater between-group similarity. Black arrows in the color bar indicate the bottom and the top 15% similarity. The figure shows that anterior VOTC regions show a high correlation between and the blind and the sighted. Adapted from Wang et al. (2015). **b** | Category selectivity in VOTC of sighted (Top; visual stimulation) and blind subjects (Bottom; auditory stimulation). (Left) Results of statistical comparisons between each category and the average response of the other categories. (Right) Unthresholded sensitivity for each of the four categories in order to visualize the functional topography of VOTC. Again, showing similarity between the blind and sighted independently from stimulation modality. Adapted from van den Hurk et al. (2017).

In a dramatic contrast to anterior VOTC, when going posteriorly towards the occipital pole, the similarity in activation profiles between the blind and sighted declines (Figure 1.4a; Wang et al. 2015). This suggests that plasticity does not impact visual regions equally. An example of such difference was well demonstrated in a magnetoencephalography (MEG) semantic priming study by Schepers et al. (2012) that used a haptic prime (e.g. rubber duck) which was followed by a semantic categorization task using typical object sounds (e.g. quack-quack). Half of the sounds were semantically incongruent object sounds (e.g. glass shattering for the rubber duck). Their results indicated an increase in induced gamma-band power in V1, thought to represent local visual processing in the sighted, only in the blind, as early as 110ms after sound presentation. In addition, they found an object-congruency effect, manifested as an increase in induced gamma-band power for incongruent sound, starting approximately 300ms after sound onset.

In the blind, as will be reviewed below, posterior regions including early visual cortex implement high-order cognitive functions in contrast to what they implement in the sighted.

1.5.5. Language processing

The most studied cognitive domain in the blind is that of language. Targeting language functions, many authors used word generation tasks. For example, asking subjects to generate a semantically associated word to presented lists of words. Compared to rest, this task activated the visual cortex bilaterally from the occipital pole ventrally and dorsally. A similar activation was observed when subjects were asked to generate a word that rhymes with a presented list of words (Burton et al. 2003). A variant task is verb generation, namely, finding an associated verb for presented words. For example, given the word “chair”, a possible response would be “to sit”. Using a task of verb generation to Braille words versus a control task of reading strings of nonexistent Braille characters where the 6 dots are embossed, Burton et al. (2002) demonstrated an extensive left-lateralized activation in the blind. The main foci were in the calcarine sulcus, the cuneus, the fusiform gyrus and the lateral occipital cortex (LOC). In a second study, authors from the same group used heard nouns as input versus a control task of listening to matched unintelligible sounds (Burton et al. 2002). The results in the second study were similar to the first, leading the authors to suggest that the visual activation could be actually driven by language functions and not by the sensory input per se. Other studies using verb generation either used low-level perceptual control conditions (e.g. unintelligible words) or basic language control conditions (e.g. repeat word) and reported largely similar results, namely, an extensive left-lateralized visual activation (Amedi et al. 2003; Ofan and Zohary 2007; Struiksma et al. 2011). This lateralization was thought to relate to the language dominance of the left hemisphere (Burton et al. 2002). Indeed, using several samples of blind

subjects, Lane et al. (2017) recently demonstrated a correlation between language lateralization in frontotemporal language regions and language-responsive occipital cortex. Furthermore, a causal role in verb generation was established for the visual cortex using repetitive TMS (rTMS). Amedi et al. (2004) were able to induce semantic errors during verb generation when stimulating the occipital pole of blind subjects. The same stimulation did not affect sighted subjects that presented similar errors when their prefrontal cortex was stimulated.

Using a variation to verb generation, Watkins et al. (2012) presented subjects with descriptive phrases such as “bees make it” to which they had to find a corresponding name, in this case “honey”. The authors studied a small group of blind subjects (n=5) with bilateral anophthalmia where both eyes fail to develop and retinal input to the visual system is completely absent. In a comparison between word-generation and a control condition of listening to reverse speech, anophthalmic subjects activated the inferior parts of the occipital cortex in addition to the LOC. Differences between the results of this study and the more extensive previous results could stem from the small group size and the different etiology (Watkins et al. 2012).

In general, however, the use of word generation for studying language could be problematic due to the variety of cognitive functions involved in executing such tasks. Especially when using low-level control conditions, activations could be attributed to executive, memory and motor processes. In an attempt to circumvent such confounding factors, Bedny et al. (2011) focused on language perception using different levels of language content coupled with a simple working-memory task. Subjects listened to stimuli from five categories: normal sentences, lists of words, jabberwocky sentences (where grammatical structure is normal but all content words are replaced with nonsense words), lists of nonsense words and an auditory control condition where sentences were played backwards. After each stimulus, a probe was presented and subjects had to judge whether the probe was part of the stimulus preceding it. The authors used contrasts of syntax (Sentences + Jabberwocky) > (Word lists + Pseudoword lists) and semantics (Sentences + Word lists) > (Jabberwocky + Pseudoword lists) in order to probe for language perception related activations. Classical language regions such as the inferior frontal gyrus (IFG) and the superior temporal sulcus (STS) were found to be activated in the sighted as well as in the blind under both contrasts. Only in the blind, however, the authors found a left-lateralized activation in the occipital pole, striate cortex and LOC (Figure 1.5Aa). In addition, the activation profile across conditions in the activated visual cortex resembled that of classical language regions. Response for sentences was stronger than the responses to lists of words and jabberwocky, which were stronger than the response to non-words (Figure 1.5Ab). Thus, Bedny et al. (2011), using high-level control conditions,

provided more ample evidence supporting the hypothesis that the visual cortex in the blind processes language. This finding has been corroborated by studying sentences with syntactic movement that require relating distant words for comprehension, e.g., “The actress that the creator of the gritty HBO crime series admires often improvises her lines”. In the sighted and the blind, sensitivity to syntactic movement was found in prefrontal and temporal language areas. However, only in the blind, it was also found in several occipital regions such as the cuneus, the fusiform and lingual gyri and the LOC. Moreover, blind subjects with greater sensitivity to syntactic movement in the LOC and the fusiform gyrus were better at understanding sentences with synaptic movement (Lane et al. 2015). Finally, using a task where subjects had to judge the equivalency of two sentences, Struiksma et al. (2011) showed that regions in the left middle occipital and lingual gyri are sensitive to linguistic load. They did not, however, find evidence supporting the involvement of the visual cortex in processing spatial terms (e.g. above, left of) which were processed in the supramarginal gyrus (SMG) in the sighted as well as the blind.

Interested in the phonetic features of language, Pishnamazi et al. (2016) showed that the blind activate the right occipital pole and lingual gyrus when listening to auditory phonemes ([pɑ], [bɑ], [kɑ], and [gɑ]) but not when reading them using Braille. Furthermore, using a repetition suppression design where subjects passively listened to the French phonemes /i/ and /y/, Arnaud et al. (2013) first showed that in addition to the activation of temporal auditory regions in the blind and sighted, the cuneus, and the parahippocampal, lingual and middle occipital gyri were activated in the blind. Second, they showed an effect of repetition suppression for phonemes in the blind that extended from the left lateral occipital cortex dorsally towards the left SMG and bilateral intraparietal sulci (Arnaud et al. 2013).

At the syllabic level, recent findings using MEG demonstrated that, in the blind, signal from the calcarine sulcus is synchronized to the temporal dynamics of intelligible human speech (Luo and Poeppel 2007; Van Ackeren et al. 2018). This finding resulted from an analysis that compared coherence measures between sound envelope and brain activity. More specifically, the authors compared the coherence between intelligible speech and unintelligible speech (with the same sound envelope) across blind and sighted. When comparing the blind to the sighted using both intelligible and unintelligible speech, the authors found synchrony only with regions centered around the precuneus (Van Ackeren et al. 2018). Taken together, those results suggest that the blind visual cortex is not only processing abstract language information, but might also play a role in its more sensory aspects.

In the domain of semantics, the N400 congruency response is a well-studied electrophysiological marker. Typically, the N400 component is larger when comparing semantically incongruent to

semantically congruent sentence endings (e.g. tomorrow, the boy will be ten years hill). It is also sensitive to word frequency, familiarity and repetition and its source has been localized to the inferior frontal and anterior temporal cortices (reviewed in Kutas and Federmeier 2011). The modulation of the N400 response by incongruous sentence endings has been also demonstrated in the blind. The effect elicited by incongruent words started earlier in the blind (75-100ms after onset) than in in the sighted (150ms after onset). Moreover, while typical scalp distributions are slightly left-lateralized fronto-central, in the blind the N400 effect was more symmetric and broader than in the sighted (Röder et al. 2000). Some evidence also suggests that an N400 congruency effect peaking at approximately 550ms could be elicited when sentences are coded in Braille (Glyn et al. 2015).

Finally, it is noteworthy to mention that preferential responses to spoken language in the visual cortex of blind children can be observed as early as by 4 years of age. Those responses precede prefrontal sensitivity to language that develops later in the blind when compared to the sighted (Bedny et al. 2015).

In summary, ample evidence supports the role of blind visual cortex in language processing. On the one hand, sensitivity to features such as semantics and syntax advocate for high-level processing. On the other hand, some evidence suggests that the blind visual cortex may also play a role in lower-level language-related processing.

1.5.6. Other symbolic representations

Blind visual cortex was also shown to be sensitive to mathematics. Kanjlia et al. (2016) compared a task where subjects had to perform algebraic calculations to assess the equivalence of two equations to a task where subjects had to assess the semantic equivalence of two sentences. In the blind, they found a double dissociation where language activated right ventral occipital-temporal cortex laterally and mathematics engaged the bilateral dorsal middle and superior occipital sulci and medial ventral occipital-temporal sulci (Figure 1.5B). This was in addition to the preserved preference for mathematics in the intraparietal sulci (IPS). The authors also showed a correlation between the behavioral toll and activation contrast of task difficulty that hints towards the functional relevance of the reorganized visual cortex in numerical cognition (Kanjlia et al. 2016).

1.5.7. Long-term memory

It is inconclusive whether or not the blind visual cortex is involved in long-term memory processes. On the one hand, it was extensively activated when subjects retrieved a previously rehearsed list of abstract words from memory (Figure 1.5Ca; Amedi et al. 2003). A year later, Raz et al. (2005) asked the same

subjects to judge if a word has been heard in the previous experiment or not and showed a comparable left-lateralized activation in the visual cortex. Both studies found a significant correlation between the level of activation in the calcarine sulcus and individual subject performance (Figure 1.5Cb; Amedi et al. 2003; Raz et al. 2005). On the other hand, several studies failed to find such activation for memory in the visual cortex during the new/old classification of neither vibro-tactile sequences (Sinclair et al. 2011) nor auditory and Braille words (Burton et al. 2012). Both studies only found a general widespread effect of task in the blind. A similar result was found using EEG where previously heard words compared to new words yielded a more positive event-related response but not in parietal-occipital electrodes (2001).

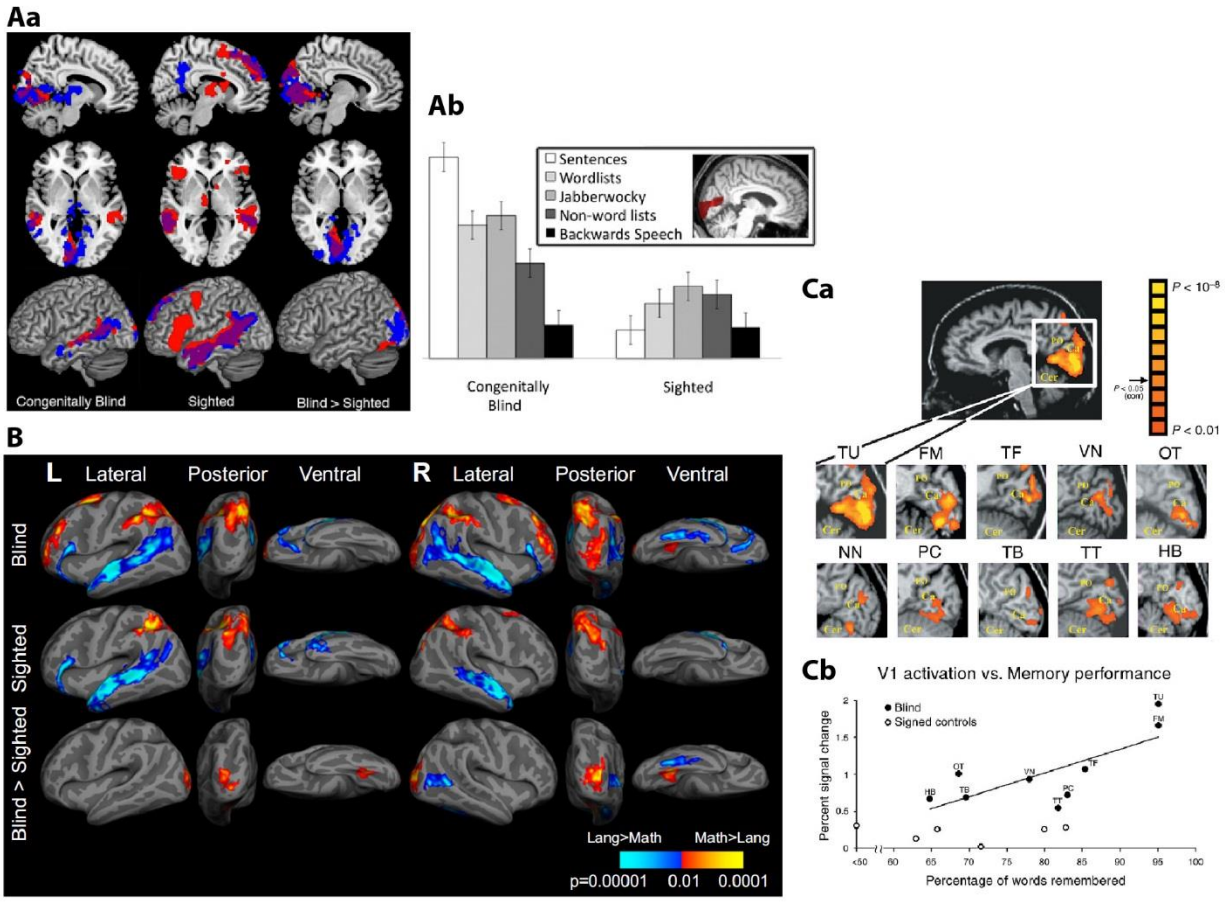


Figure 1.5 – Visual activation by high-order cognitive functions. Aa | Activation during a language task in the blind, sighted and a comparison between blind and sighted. In red, a contrast of syntax (Sentences + Jabberwocky) > (Word lists + Pseudoword lists) and in blue, a contrast of semantics (Sentences + Word lists) > (Jabberwocky + Pseudoword lists). The figure shows that the blind activate the occipital cortex in addition to classical language regions in the lateral temporal cortex. **Ab** | Activation levels in V1 of the blind and the sighted showing a modulation by the amount of semantic and syntactic information. Adapted from Bedny et al. (2011). **B** | Brain regions active for mathematics > language (warm colors) and language > mathematics (cool colors) in the blind, sighted and a comparison between the two groups. The figure shows a double dissociation between activation for mathematics in posterior regions and language in inferior ventral regions. Adapted from Kanjlia et al. (2016). **Ca** | Group and single-subject activation in the blind during retrieval of lists of abstract words from memory. **Cb** | Performance in memory retrieval out of the scanner plotted against percent signal change in V1 showing a positive correlation between performance and activation only in the blind. Adapted from Amedi et al. (2003).

1.5.8. Executive functions

An attentional modulation in the visual cortex of the blind was suggested upon findings of more posterior scalp distributions of attentional markers. Using event-related potentials (ERPs), Alho et al. (1993) showed that the processing negativity, an index of auditory selective attention is more posterior in the blind than in the sighted. This result was confirmed using MEG, where subjects were either asked to attend auditory input and count rare changes in pitch or to read a text in Braille without paying attention to the auditory input. Activity to deviant sounds in the attended condition was present in both groups in the auditory cortex approximately 100-200ms after onset. However, only in the blind, attention-related activity was present in the visual cortex approximately 300-400ms after stimulus onset (Kujala et al. 1995). Those results were further expanded by Liotti et al. (1998) which showed that in contrast to the neural correlates of sustained attention and the mismatch negativity (MMN) response which were similar in the blind and sighted, late target selection significantly differed between the groups. Those differences were most remarkable during 200-300 msec after onset above the parietal cortex and during 300-450 msec above the occipital cortex. This result was interpreted as visual cortex involvement in task-relevant auditory processing (Liotti et al. 1998). A similar conclusion was reached by Röder et al. (1996) that used an odd-ball task with auditory and tactile stimuli. They found a slow negative shift in the blind over the occipital cortex that did not depend on the stimulus modality which they interpreted as non-specific attention-related processing. Also using an oddball paradigm, Weaver et al. (2007), using fMRI, showed sensitivity to salient target and distractor stimuli in the calcarine sulcus, lingual and fusiform gyri and cuneus for both auditory and tactile stimulation. They argued that those regions are involved in attention reorientation and proposed their involvement with the ventral fronto-parietal attention network. The authors also tested selective attention to one sensory modality during simultaneous auditory and tactile stimulation. When attending to the auditory modality, only auditory targets elicited an effect in the calcarine sulcus, lingual gyrus and cuneus. However, when attending to the tactile modality, an effect of tactile targets was only weakly observed in the calcarine sulcus. This finding exposes a complex interaction of attention and input modality in the visual cortex in the blind (Weaver and Stevens 2007). Finally, Stevens et al. (2007) showed that cued preparatory responses for an auditory task were present in the calcarine sulcus and the lingual gyrus only in the blind. A shift in baseline BOLD activity was observed in those regions when subjects were cued for an upcoming trial when compared to being cued to a no-trial. This lies, the authors suggested, in similarity to the preparatory activity in the visual cortex that is elicited by visual cues (Stevens et al. 2007).

Concerning non-attentional executive effects, previous studies in the blind targeted working memory. Using tactile stimulation and comparing tasks of one-back frequency change to within-trial amplitude change, Burton et al. (2010) failed to find significant difference in the visual cortex of the blind. They did, however, find such effects in the dorsolateral prefrontal cortex of the same subjects. Some authors suggested that visual cortex of the blind may be involved in executive processing based on functional connectivity by showing that prefrontal regions with altered functional connectivity to the occipital cortex in the blind could be activated by working-memory load (Deen et al. 2015a). To the best of my knowledge, no direct demonstration of non-attentional executive processing in the visual cortex of the blind has been published.

To summarize the involvement of the blind visual cortex in cognitive functions: there is compelling evidence for language processing and modulation by attention; initial evidence for mathematics; a less clear picture for long-term memory; and last, no direct evidence for executive processing.

1.6. Connectivity of the visual cortex

The novel functional engagement of the blind visual cortex entails it is able to receive non-visual information. This information could either be channeled through normal or altered connections in the brain. Using anatomical and functional connectivity techniques, several studies probed the connectivity differences between the blind and the sighted.

Anatomical connectivity, based on diffusion tensor imaging (DTI), exploits the diffusion of water molecules in neurons in order to reconstruct their anatomical layout (Basser et al. 2000). This enables comparing gross scale anatomical differences between groups. When comparing the blind to the sighted, Shimony et al. (2006) found a decrease in connectivity between the lateral geniculate nucleus (LGN) and the visual cortex with connectivity from the visual to prefrontal and temporal cortices largely preserved. However, most interestingly, they failed to find any new tracts that are specific to the blind. Those results could mean that information reaches the blind visual cortex through existing neuronal channels (Shimony et al. 2006). However, using voxel-based morphometry on anatomical (non-diffusion) images, Ptito et al. (2008) reported an increase in white matter volume in the occipito-frontal and superior longitudinal fasiculi, suggesting an increase in connectivity between occipital and prefrontal cortex. They also found a decrease in white matter volume in the splenium of the corpus callosum, suggesting a decrease in inter-hemispheric connectivity of the occipital cortex in blindness (see however studies that failed to find such differences; Shimony et al. 2006; Bock et al. 2013). It should be noted

that limitations such as small sample sizes and high variability between individuals may underlie negative or contradictory findings using those anatomic techniques (Bock and Fine 2014).

Functional connectivity, on the other hand, is based on the co-activation of brain regions at rest which is thought to reflect frequent co-activation during normal activity (Fox and Raichle 2007). In contrast to anatomical connectivity, studies probing functional connectivity changes due to blindness are abundant and relatively consistent in their findings. First, a decrease in inter-hemispheric connectivity was observed in the visual cortex of the blind. Second, a decrease in connectivity between early visual areas and auditory, somatosensory and motor areas. Third, an increase in connectivity between the visual cortex and the lateral prefrontal, parietal and temporal cortices (Liu et al. 2007; Yu et al. 2008; Bedny et al. 2011; Watkins et al. 2012; Butt et al. 2013; Qin et al. 2013; Burton et al. 2014; Wang et al. 2014; Deen et al. 2015b; Striem-Amit et al. 2015).

Moreover, investigating activity at rest using MEG showed increased correlations between primary and secondary visual cortex (V1 & V2) and the rest of the brain in the delta (1-3 Hz) and gamma (76-128 Hz) bands when comparing the blind to the sighted. Also, gamma-band activity in the blind visual cortex was found to be phase-amplitude coupled to the delta-band activity indicating functional involvement even at rest. This was in contrast to the sighted where gamma-band activity was phase-amplitude coupled to the alpha-band activity, indicating functional inhibition (Hawellek et al. 2013). Those diverging signatures are interpreted as evidence to the essentially different processes taking place in the blind and sighted visual cortices.

Complementing the above findings is a fine-grain analysis of the connectivity profile (to the rest of the brain) in the ventral stream of the visual cortex where more posterior regions exhibited a different profile between blind and sighted while more anterior regions exhibited similarity between the groups. Moreover, anterior regions with similar connectivity profiles between blind and sighted also showed similarity in activation pattern (between the groups) to nouns from 16 different semantic categories. This is in contrast to posterior ventral regions that showed a different activation profile between blind and sighted (Wang et al. 2015). Those results indicate that alterations in function and alterations in connectivity might be related.

Relating alterations in connectivity to the functional reorganization of the visual cortex is possible by probing the network involvement of functionally defined regions of interest. For example, Bedny et al. (2011) showed that language-sensitive regions of interest in the medial and lateral occipital cortex had increased connectivity to inferior frontal gyrus, inferior frontal sulcus and middle frontal gyrus with language-sensitivity in the sighted.

More generally, increased functional connectivity between occipital and dorsolateral prefrontal cortex in the blind lead authors to suggest that the visual cortex might be processing classically prefrontal computations as a result of visual deprivation (Burton et al. 2014). However, others rejected such suggestions citing the non-specific extent of those alterations widely connecting the prefrontal to most of the occipital cortex (Bock and Fine 2014). In contrast to this rejection are results obtained by Watkins et al. (2012) in anophthalmic subjects with networks of voxels co-activated at rest extracted using independent component analysis (ICA). The authors showed that language-sensitive regions in LOC were incorporated into a 'language' network comprising of inferior frontal gyrus, medial superior frontal cortex and angular gyrus in the sighted. The fact that those networks were extracted using ICA implies that they share a certain amount of unique variance that is not common to all visual regions. Thus, pointing to a certain degree of specific connectivity between visual and frontotemporal regions. More directly, Kanjlia et al. (2016) compared the network involvement of language-sensitive and mathematics-sensitive regions in the visual cortex of the blind. They found that language-sensitive regions were more connected to language processing areas in the prefrontal cortex and mathematics-sensitive regions were more connected to areas involved in mathematical computations in the parietal cortex.

Last, we are faced with a "Chicken-and-egg" dilemma where it remains an open question whether connectivity precedes, and therefore leads to, the recruitment of the visual cortex or develops with it hand in hand. In this regard, it was recently suggested that, during development, innate connectivity patterns constrain cortical specialization for potentially pluripotent cortex. Therefore, with the lack of visual input, innate connectivity to parietal cortex would recruit dorsal visual cortex for numerical and spatial abilities whereas the language faculty would occupy ventral visual cortex through its connectivity to temporal and prefrontal cortex (Bedny 2017).

1.7. Summary and thesis outline

Through this introduction, I portrayed the engagement of the blind visual cortex in various functions. This engagement is unlikely to be epiphenomenal because it reflects behavioral measures and was found necessary for computation in brain stimulation studies. Some of the functions activating the blind visual cortex are completely alien to its normal counterpart, others are presumed to have shared functionality with visual processing. Hence, in a brief schematic summary: as a result of blindness, posterior regions of the visual cortex tend to adopt novel computations whereas anterior ventral regions and superior dorsal regions show macro-level functional equivalence to the sighted. Accompanying this functional profile are alterations in connectivity to the rest of the brain.

In the current thesis, I focus on the novel cognitive functions executed in the blind visual cortex. An initial review of the literature revealed that most studies focused on single functions, allowing only inter-study comparisons. This motivated studying the mosaic of functional preference in the reorganized blind visual cortex. Therefore, we proceeded to testing blind and sighted subjects with cognitive tasks that hold potential to activate the blind visual cortex. Those covered the domains of language (perception and generation), memory and executive control. In addition, we also wished to explore the correspondence between this putative mosaic and the reported alterations in the connectivity profile of the blind visual cortex **(Chapter 2)**. We found that all tested functions activate the blind visual cortex. Crucially, we also found that visual regions activated by specific functions also entertain distinct connectivity to brain networks supporting those functions. Curious about the origins of this functionally-relevant connectivity, we attempted to answer the "Chicken-and-egg" question. What came first, the activation or the connectivity? We hypothesized that the egg preceded the chicken, namely, that regions engaged in cognitive processing in the blind visual cortex possess innate connectivity to the temporal and prefrontal cortices constraining their eventual activation profile. Somewhat naively, we tested this hypothesis using a publically available resting-state dataset of neonates **(Chapter 2, Section 2.2)**.

Finally, taking a step away from the macro-level organization, we focused on the processing of language information in the blind visual cortex seeking to understand whether the general sensitivity to semantics found in the literature entails the coding of semantic category. Therefore, we probed the spatiotemporal unfolding of semantic processing in the blind and the sighted **(Chapter 3)**.

2. Cognitive functions of the visual cortex in the blind

In this chapter, we address the organization of cognitive functions in the visual cortex of the blind and the correspondence between this organization and long-distance connectivity. We used speech comprehension and word generation to investigate language, task-switching to investigate executive control and incidental long-term memory to investigate memory. In each paradigm, we defined tight contrasts of interest that controlled, as much as possible, for low-level parameters. This allowed us to delineate regions activated by circumscribed high-level functions. Then, we asked whether those regions would show distinct connectivity profiles that are related to the novel functions they execute (Section 2.1).

Having found confirmatory results, we then tested whether connectivity biases present at birth could explain the brain reorganization in the blind (Section 2.2). Finally, we conclude this chapter with a short discussion on the limitations of those studies and future perspectives (Section 2.3).

2.1. Distinctive expansion of cognitive networks into the visual cortex in the blind

Distinctive expansion of cognitive networks into the visual cortex in the blind

Sami Abboud[1,2], Laurent Cohen[1,3]

[1] Inserm U 1127, CNRS UMR 7225, Sorbonne Universités, UPMC Univ Paris 06 UMR S 1127, Institut du Cerveau et de la Moelle épinière, ICM, F-75013, Paris, France

[2] Inserm U968, CNRS UMR 7210, Sorbonne Universités, UPMC Univ Paris 06, Institut de la Vision, F-75012, Paris, France

[3] Service de Neurologie 1, Hôpital de la Pitié Salpêtrière, AP-HP, F-75013, Paris, France

Running title: Cognitive functions in the blind visual cortex

Corresponding author:

Sami Abboud

Institut du Cerveau et de la Moelle épinière

47 Boulevard Hôpital, 75013 Paris, France

Phone: +33 (0)1 57 27 42 37

E-mail: s@mi.nalisa.net

Abstract

In the early blind, brain activation by a variety of non-perceptual cognitive tasks extends to the visual cortex, while in the sighted it is restricted to supramodal association areas. We hypothesized that such activation results from the integration of different sectors of the visual cortex into typical task-dependent networks. We tested this hypothesis with fMRI in the blind and sighted using tasks assessing speech comprehension, incidental long-term memory and both verbal and non-verbal executive control, in addition to collecting resting-state data. All tasks activated the visual cortex in the blind relative to the sighted, which enabled its segmentation according to task sensitivity. We then assessed the unique brain-scale functional connectivity of the segmented areas during resting state. Language-related seeds were connected to frontal and temporal language areas; the seed derived from the executive task was connected to the right dorsal frontoparietal executive network; the memory-related seed was uniquely connected to mesial frontoparietal areas involved in episodic memory retrieval. Thus, using a broad set of language, executive, and memory tasks in the same subjects, combined with resting state connectivity, we demonstrate the selective integration of different patches of the visual cortex into brain-scale networks with distinct topography, lateralization, and functional roles.

Keywords

Blindness, Cognitive functions, Network reorganization, Plasticity, Visual system

2.1.1. Introduction

About one third of the human cortex is commonly labelled as visual. However, imaging studies in sighted humans have shown that some of those regions also carry out multisensory computations and high-order perceptual functions from non-visual input, which persist in the early blind (Ricciardi et al. 2014; Murray et al. 2016). Beyond perception, there is functional imaging evidence that in the early blind (EB), the visual cortex may acquire a novel role in supporting non-perceptual functions (Cecchetti et al. 2016). The scope of such non-perceptual recycling is large and includes language (Sadato et al. 1996; Amedi et al. 2003; Bedny et al. 2011), mathematics (Kanjlia et al. 2016), memory (Raz et al. 2005; Burton et al. 2012) and activations that may relate to executive functions (Burton et al. 2010; Lewis et al. 2010; Deen et al. 2015). Those activations are unlikely to be epiphenomenal as several studies showed that they correlate with performance measures across participants (Amedi et al. 2003; Gougoux et al. 2005; Lane et al. 2015). Accordingly, transcranial magnetic stimulation and lesion studies showed that disrupting the activated areas yields cognitive deficits in blind subjects (Cohen et al. 1997; Hamilton et al. 2000; Amedi et al. 2004). Moreover, the functional connectivity of the visual cortex with the rest of the brain differs from that of the sighted. There is, generally, a decrease in inter-hemispheric occipital connectivity, a decrease in visual to auditory and somatosensory connectivity, and an increase in connectivity between the visual cortex and the lateral prefrontal, parietal and temporal cortices (Liu et al. 2007; Yu et al. 2008; Bedny et al. 2011; Watkins et al. 2012; Butt et al. 2013; Qin et al. 2013; Burton et al. 2014; Wang et al. 2014; Deen et al. 2015; Striem-Amit et al. 2015, see however, Heine et al., 2015).

How are those alterations in functional connectivity related to the novel cognitive functions acquired by the visual cortex in the blind? The goal of this study is to determine whether areas activated by non-perceptual functions in the visual cortex of the EB show functionally relevant brain-scale connectivity.

Addressing a similar question, Kanjlia et al. (2016) recently showed that distinct visual regions are activated by language and mathematics in the blind. Those two regions were also preferentially connected to distant areas processing language and mathematics, respectively.

In the present study, we assess whether this phenomenon is a more general feature of the visual cortex of the blind. To this end, we use a diverse series of high-level non-perceptual cognitive tasks combined with functional connectivity measures: A task switching paradigm directly assessing executive control, a speech perception task focusing on language comprehension, an incidental memory task targeting retrieval from long-term memory and a more composite word generation task assessing verbal executive functions. The objective of using both novel and more customary paradigms is to portray a more elaborate description of the functional recruitment of the visual cortex in the blind.

We predicted that: (1) all high-level cognitive tasks should elicit activations in the visual cortex of the blind, as compared to sighted controls; (2) areas activated by different tasks should be connected to distinct functional networks reflecting the novel involvement of the visual cortex in language, memory and executive functions. In a first step, we studied the activation elicited during the different tasks. In a second step, we used resting-state data in the same subjects, to identify the brain-scale functional networks specifically connected to the activated areas.

2.1.2. Materials and methods

Subjects

The study included 12 early blind subjects (age: 44±12, mean±SD) and 16 sighted control subjects (age: 42±12), out of which 12 were matched in sex and age to the blind group. All subjects were native French speakers. All blind subjects were blind from birth and had any form of light perception (Table 1). One blind subject was excluded from the analysis due to anomalies in brain anatomy. All subjects signed an informed consent form, were paid for their participation, and were naïve about the aims of the study. The experiment was approved by the local ethical committee.

Table 1 – Causes of blindness

Subject code	Sex	Age	Cause of blindness
B1	M	25	Congenital bilateral glaucoma
B2	F	28	Micropthalmia
B3	F	54	Bilateral retinopathy of prematurity
B4	M	48	Retinal detachment
B5	F	43	Micropthalmia
B6	M	66	Congenital retinis pegmintosa
B7	M	51	Unknown
B8	F	44	Bilateral retinopathy of prematurity
B9	F	44	Bilateral retinopathy of prematurity
B10	M	44	Unknown
B11	F	31	Congenital bilateral glaucoma

fMRI experimental paradigms

Each subject went through 2 magnetic resonance imaging (MRI) sessions performed on two separate days. This allowed us to acquire a high-resolution anatomical image (T1) and functional MRI (fMRI) data during 4 activation experiments and during a resting state run. Before acquisition, subjects participated in short training sessions outside the magnet, during which they performed a few training blocks of the upcoming paradigms. All subjects were blindfolded throughout the MRI acquisitions and were instructed to keep their eyes closed.

Cognitive activation experiments

Speech perception

In order to localize the brain regions involved in processing semantics and syntax, we designed a speech perception paradigm in which subjects attended to words and pseudo-words arranged either in sentences or in lists. The 4 types of stimuli were built as follows. Sentences consisted of 96 French sentences ranging from 9 to 12 words (e.g. “Il compte les mots qui couvrent la page du journal”). Word lists were derived from the sentences by shuffling the words (e.g. “La compte les du Il journal page couvrent qui mots”). So-called Jabberwocky stimuli were derived from the sentences by keeping intact the original order of words as well as grammatical morphemes, while replacing the other words with phonologically matched pseudo-words, respecting the original sentence prosody (e.g. “Il sige les fleux qui dasent la plite du gornion”). Pseudo-word lists were derived from the jabberwocky condition by shuffling (e.g. “La sige fleux du plite dasent qui les gornion il”). The 384 (96 x 4) stimuli were recorded by a male native French speaker, and processed with Audacity. Noise removal and normalization (maximum amplitude set to -1.0dB) were applied to the recordings. All stimuli were then duplicated and a pitch change (10% upwards, without changing speed) was applied to the duplicated set in order to generate the same stimuli with a higher-pitch voice. High-pitch stimuli were used only as targets in a difficult voice change detection task aiming at maintaining the subjects’ attention to the stimuli. In order to avoid repetition effects between a sentence and the corresponding shuffled list, stimuli were then split into two sets of 48 stimuli per category (sets A and B). Two groups of stimuli were then created: a group consisting of sentences from set A and lists from set B (group 1) and conversely (group 2). Subjects were randomly assigned to one of the two groups.

Subjects received 16 blocks of each of the 4 categories. Blocks with a duration of 12 s were arranged such that each block contained 3 stimuli and an inter-stimulus silence of 0.6 s. For each condition, 3 blocks out of 16 were selected at random in which one stimulus was substituted by its high-pitched counterpart. Subjects had to press the left button as soon as they detected this voice change. Due to the

varying duration of the stimuli and in order to form blocks homogenous in duration, we adjusted the duration of stimuli in the range of -5% to 7%, without changing their pitch. In order to equate the duration of blocks, we grouped stimuli into blocks using an optimization algorithm (constrained linear least-squares solver) for each condition. A pseudo random order of the blocks was generated for each subject. No more than 2 consecutive blocks of the same condition were allowed. Each block ended with a rest period (2 s), and 24 blocks of rest (10 s) were randomly distributed among the task blocks. The experiment was divided into 2 equal runs (9 m 43 s each) to minimize fatigue and movement. Each run started and ended with additional rest periods (20 s and 10 s, respectively). Blocks were tagged as erroneous if the subject either failed to detect the change in the speaker voice, or signaled a change when there was none. The effects of semantics were assessed using a contrast of (Sentences + Word-lists) minus (Jabberwocky + Pseudoword lists). The effects of syntax were assessed using a contrast of (Sentences + Jabberwocky) minus (Word-lists + Pseudoword-lists).

Word generation

In order to probe verbal executive processing, we used a word generation paradigm. Subjects were presented with auditory nouns, and had to overtly generate words according to 3 tasks: Repeat, where subjects had to repeat the heard noun (e.g. cheese -> cheese), Verb, where subjects had to generate a verb associated to the heard noun (e.g. cheese -> to eat), and Initial, where subjects had to generate a word starting with the same phoneme as the heard noun (e.g. cheese -> children). Stimuli consisted of a set of 70 French nouns selected from the Lexique database (New et al. 2004). Instructions consisted of the words “répéter”, “verbe”, and “initiale”. Stimuli and instructions were synthetically generated using the Text-to-Speech function built in OSx 10.9.5 (Apple Inc., CA, United States).Subjects received 14 stimulation blocks for each of the 3 conditions. Each block started with an instruction word (2 s), followed by 5 trials (3 s each) including stimulus presentation and response time-window, and ended with a resting period (3 s), totaling 20 s per block. Pseudo-random permutations of stimuli and block types were generated for each subject. No more than 2 consecutive blocks of the same condition were allowed, and subjects received all 70 words under the 3 conditions. In addition, 18 rest blocks (12 s) were randomly distributed among the stimulation blocks. The experiment was divided into 2 equal runs (9 min 6s each) to minimize subject fatigue and movement. Each run started and ended with an additional rest period (20s and 10s, respectively). Subjects were instructed to produce an overt response after each trial, speaking with a normal voice while maintaining their head still. Responses were recorded for subsequent scoring of errors. Recordings were denoised so as to remove the scanner noise, and latencies were computed as the lag between the onset of stimuli and the onset of vocal responses.

This lag was verified and, when needed, corrected manually for all trials. Spurious preverbal noises were manually excluded from the computation of latencies. Trials on which subjects either did not respond in the designated time-window or produced a response that did not comply with the current instruction were flagged as errors and excluded from the response time analyses. One blind subject with excessive head motion and two sighted subjects tested with different scanning parameters were excluded from the analysis of this experiment. The effects of word generation were assessed using the Verb minus Repeat and Initial minus Repeat contrasts. We hypothesized that the Initial task would be more effortful than the Verb task due to the need for an active lexical search when compared with the Verb task which is more associative in nature, thus, resulting in a differential brain response.

Executive control

We used an auditory adaption of a contextual task-switching paradigm sensitive to task-set reconfiguration costs, the process of manipulating stimulus-response rules (Koechlin et al. 2003; Monsell 2003). Trials consisted of one French vowel ([a],[i], or [u]) followed by a series of 3 or 4 different notes played on the piano, forming an ascending or a descending scale. On each trial, the initial vowel specified the task to be performed. For vowel [a], the task was to judge whether the upcoming series contained 3 or 4 notes, and to respond with a left or a right button press, respectively. For vowel [u], the task was to judge whether the scale was descending or ascending, and to respond with a left or a right button press, respectively. Finally, for vowel [i], no response was to be made. The [a], [u], and [i] vowels were recordings (500 ms) of a male human voice, normalized and low-pass filtered (3500 kHz). Piano notes were generated using the Grand Piano instrument in Kontak 4 (Native Instruments GmbH, Germany). The notes were C2, E2, G#2, C3, E3, G#3, C4, and their duration was 125 ms. The full set of stimuli thus included 12 different items: 3 tasks x 2 numbers of notes x 2 melodic contours. Those items were used to build trials for the 3 experimental conditions: Number blocks which included only [a] and [i] trials; Melody blocks which included only [u] and [i] trials; and Mixture blocks which included all 3 possible tasks (i.e. [a], [u], and [i]). Each block started with the synthetically generated instruction word “nombre”, “mélodie”, or “mélange”. Subjects received 8 blocks of Number and 8 blocks of Melody (which will be referred to as Single-task blocks), and 16 blocks of Mixture (which will be referred to as Dual-task blocks). Each block thus began with an auditory instruction (2s), followed by 9 trials (3 s each) during which a vowel and a series of notes were played. Each block ended with 2 s of rest, for a total of 31 s. For each subject, a pseudorandom permutation of block order was generated. No more than 2 consecutive blocks of the same condition were allowed. In addition, a rest block (10 s) preceded each task block. Several constraints were enforced when generating the random order of the stimuli within

blocks: 1) A block cannot start with an 'i' stimulus (no response), 2) No consecutive 'i' stimuli are allowed, 3) No more than 2 consecutive 'a' or 'u' stimuli are allowed, 4) The number of left and right presses are equal in each block, 5) The number of congruent trials (same button for the Number and Melody tasks) and incongruent trials (different button for the two tasks) are equal in each block. The experiment was divided into 2 equal runs (11 min 1 s each) to minimize fatigue and movement. Each run ended with an additional rest period (10 s). Subjects held a response button in each hand and were instructed to respond as soon as they could without compromising performance. Response time was defined as the lag between stimulus onset and button press. Whenever subjects failed to respond in the designated time window, pressed the wrong button, or responded in the no-response condition (i.e. on trials with a [i] vowel), trials were tagged as errors and excluded from the response time analyses. One blind and one sighted subjects with excessive head motion and two sighted subjects with different scanning parameters were excluded from the analysis of this experiment. The effects of non-verbal executive control were assessed using the Dual-task minus Single-task contrast.

Long-term memory

In order to localize regions involved in long-term memory, we used an incidental long-term memory paradigm, in which subjects were asked to judge, when presented with sentences, whether they had previously heard them or not. A variant of the old/new recognition task, it is often used in order to reveal brain regions involved in retrieval from episodic memory (Konishi et al. 2000; Rugg and Henson 2002; Spaniol et al. 2009). There were 2 experimental and 2 baseline conditions in the memory experiment. Experimental conditions: Old sentences that subjects had heard as part of the Sentence condition of the speech perception experiment; New sentences that had never been presented before. Baseline conditions: Instruction sentences asking subjects to press a button, for each one of the two response buttons (e.g. "Merci d'appuyer maintenant sur le bouton de droite"). Subjects were not aware of the existence of this experiment beforehand so they would not engage in active encoding during the Speech perception experiment. It was introduced 15 minutes after the speech perception experiment, during which anatomical images were acquired. Using sentences from the speech perception experiment created a double benefit. First, it allowed probing the activation by similar perceptual input under different tasks. Second, it eliminated the need to explicitly teach subjects a new set of stimuli, a time consuming process that would have reduced testing time.

The material comprised 60 sentences taken from the speech perception experiment and 60 new sentences (recorded and processed as previously described). For each old sentence, a new sentence was created by using the structure of the former with changes limited to the content (e.g. "La maison où

habite cet homme est très abîmée" became "La forêt où vivent ces oiseaux doit être abattue"), thus achieving a matching in syntax and number of words (New: 9.8±1.8, Old: 9.9±1.4 (mean±sd); t(59)=-0.75, p=0.43, paired t-test). There were 10 instruction sentences (5 for each button side). Stimuli were divided into two groups following the division in the speech perception experiment, so as to match the specific set of sentences which each subject had heard before. We used a fast event-related design, with 30 sentences for each condition. Each trial had a total duration of 5.5 s, and consisted in a sentence, followed by a GO signal (a short ringing sound; 250 ms) and the response time-window. Subjects were instructed to respond by pressing the right-hand button for old sentences and the left-hand button for new sentences. In the Instruction condition, subjects had to obey the auditory instruction and press accordingly. The Instruction sentences asking to press left (right) were used as a baseline condition for the new (old) sentences. A pseudorandom order of events was generated for each subject with no more than 2 consecutive trials of the same condition allowed. 27 periods of rest (6 s) were distributed among the task trials. The experiment was conducted in one run (11 min 12 s), which started and ended with additional rest periods (10 s and 5 s, respectively). Trials were classified according to subject response. Old sentences that were correctly detected were classified as hits, old sentences that were identified as new were classified as misses, new sentences that were identified as such were classified as correct rejections and new sentences that were identified as old were classified as false positives. Only correctly classified trials were used for assessing the brain response in this experiment. Data from one blind subject that failed to comply with task instructions and from two sighted subjects that made 8/30 and 15/30 mistakes in the Instruction conditions were excluded from the analysis of this experiment. The general effects of the memory task were assessed using the Hits minus Instruction contrast. The effects of retrieval from long-term memory were assessed using the Hits minus Correct rejections contrast after subtraction of their respective Instruction conditions.

Experimental setup

Stimulation methods

We used Psychophysics Toolbox Version 3 (Brainard 1997; Pelli 1997; Kleiner et al. 2007) for MATLAB (Release 2011a The MathWorks, Inc., Massachusetts, United States) to implement the experimental design. The auditory stimuli were relayed to an MR Confon Easy 04 amplifier which was connected to MR Confon HP SI 01 headphones (MR confon GmbH, Germany). Subject vocal responses were recorded using either an Optoacoustics FOMRI III microphone (Optoacoustics Ltd., Israel) or a Sennheiser MO 2000 set (Sennheiser Electronic GmbH & Co., Germany). The microphone was attached to the head coil

and was placed at an approximate distance of 1 cm from the subject's mouth. All subjects wore foam earplugs and blindfolds prior to installation in the scanner.

Testing sessions

The first session included (i) a T1 anatomical volume, (ii) fMRI images during resting state, (iii) the two runs of the executive control experiment, and (iv) the two runs of the word generation experiment. The second session included (i) the two runs of the speech perception experiment, (ii) T1 and T2 anatomical volumes, (iii) the long-term memory experiment.

Behavioral data analysis

In the word generation and executive control experiments, median latencies and individual error rates were entered into ANOVAs with task as within-subject factor, group as between-subject factor and subjects as random factor. Post-hoc paired t-tests were used to compute differences between conditions in each group. In the speech perception experiment, unpaired t-tests were used to compare the groups on error rates. In the long-term memory, one-sample t-tests were used to compare d' values to chance and an unpaired t-test was used to compare the d' values between the groups.

fMRI acquisition and analysis

Imaging parameters

Anatomical and functional brain images were acquired using a 3-tesla MRI (Verio, Siemens AG, Germany). Using a 32-channel head coil, we acquired a three-dimensional T1-weighted anatomical volume (MP RAGE sequence, TR=2300ms, TE=3.1ms, flip angle=9°, 0.8mm iso-voxel resolution) and a 10 minutes series of whole-brain resting-state BOLD sensitive images (gradient-echo (GE) echo planar imaging (EPI) sequence, 45 slices, slice thickness/gap =3/0.6mm, FOV 192 x 192mm, A>>P phase encoding direction, TR=2500ms, TE=30ms, flip angle=80°). For all activation experiments, we used a 12-channel head coil, to acquire a whole-brain BOLD sensitive contrast (GE-EPI sequence, 40 slices, slice thickness/gap=3/0.3mm, FOV 204 x 204mm, A>>P phase encoding direction, TR=2020ms, TE=25ms, flip angle=80°).

Data analysis

Preprocessing

Preprocessing was performed using SPM12 (http://www.fil.ion.ucl.ac.uk/spm/) and MATLAB (Release 2014b). Anatomical volumes were segmented and normalized to the standard Montreal Neurological Institute (MNI) stereotactic space. All functional time-series were slice-time corrected, motion corrected to the mean functional imaging using a tri-linear interpolation with six degrees of freedom, co-registered

to the anatomical volume of the first session, normalized, resampled (to 3mm cubic voxels), and spatially smoothed (5mm FWHM, isotropic). Resting-state functional volumes were further preprocessed using CONN toolbox (Whitfield-Gabrieli and Nieto-Castanon 2012) in order to bring spurious correlations to a minimum. We applied linear trend removal to correct for signal drift and band-pass filtering (0.008-0.09Hz) to reduce non-neuronal contributions to the spontaneous BOLD fluctuations. Moreover, we used the aCompCor strategy (Behzadi et al. 2007) in addition to the estimated subject motion parameters (6 rigid-body head motion parameter values – x, y, z translations and rotations) to define temporal confounding factors. Finally, in order to control for between-group motion differences (Van Dijk et al. 2012), we compared the maximum absolute head motion value between the sighted and blind groups and found no significant difference ($t(22)=0.43$, $p=0.67$, unpaired t-test).

Analyses of activation paradigms

For the single-subject analyses, we used general linear-models (GLM) with paradigm specific regressors, in addition to 6 motion parameters and a high-pass filter (128 s cutoff, except in the case of the word generation paradigm, where it was set to 330 s). A boxcar function using the onsets and durations of the following predictors was convolved with a canonical hemodynamic response function (HRF) to generate the GLM regressors. Speech perception experiment: one regressor for each of the 4 conditions, plus one regressor for target sentences and one for button presses. Word generation experiment: one regressor for each of the 3 conditions plus one regressor for instructions. Executive control experiment: one regressor for each of the 3 conditions plus one regressor for instructions. Long-term memory experiment: one regressor per response class, i.e., hits, misses, correct rejections and false positives, one regressor per instruction condition, i.e., right and left plus two regressors for left and right button presses. For second-level group analyses we used one-sample t-tests for inferences on a single group of subjects, and one-way ANOVAs to assess differences or conjunctions involving the two groups. A voxelwise threshold was set to $p<0.001$ for the word generation and speech perception experiments, and $p<0.005$ for the long-term memory and executive control experiments. A clusterwise threshold of $p<0.05$ corrected across the whole brain was used. To achieve correction, the following steps were applied: The square-root of the residuals image of the GLM result of each subject was computed using 3dcalc (AFNI). Image smoothness was estimated using 3dFWHMx (AFNI) for each subject, assuming it follows a mixed autocorrelation function (ACF) and not a simple Gaussian ACF (Cox et al. 2017). The average smoothness of the group under investigation (sighted, blind, or sighted and blind together) was then used in a Monte Carlo simulation (10,000 iterations; 3dClustSim), to compute a minimal cluster size

k for each second-level result. This k value calculation corresponded respectively to k=25, 23, 25 in the sighted, the blind and both groups together in speech perception; k=24, 25, 23 in word generation; k=80, 92 and 87 in executive control; and k=80, 73, 76 in long-term memory.

Functional connectivity analysis

One representative contrast from each activation experiment was used in a functional connectivity (FC) analysis on the resting-state data (Fox and Raichle 2007). Seed regions were defined by intersecting the activation map (in the blind) of each representative contrast with a mask of the visual cortex. The mask included the gray-matter voxels of bilateral hOc1-2, hOc3v/d, hOc4v/d/la/lp, hO5 and FG1-4 (Anatomy Toolbox, Eickhoff et al. 2005) in addition to the middle and superior occipital gyri (AAL, Tzourio-Mazoyer et al. 2002). Activation maps were clusterwise corrected ($p<0.05$) across the whole brain following voxelwise thresholding ($p<0.001$ for all maps except for the Executive Control contrast where $p<0.005$). Moreover, all activated voxels constituting the seed regions are also voxel-wise FDR corrected ($q=0.05$) in the visual cortex mask (Figure 2). FC was computed as follows. For each subject, the average time-course of the preprocessed resting-state BOLD signal was extracted from each seed region, and a whole brain correlation map was computed. Correlation values were then transformed into Z values (Fisher's r-to-Z). For each seed, the individual Z-maps were entered in a second-level group analysis where the blind and sighted groups were compared resulting in a t-map of connectivity differences (CONN toolbox). Next, in order to generate group-level functional connectivity maps representing the unique connectivity of each seed, we used semi-partial correlation coefficients. For each seed, those coefficients result from a correlation analysis of its time-course while regressing out the time-courses of all other seeds. In other words, semi-partial correlations depend only on seed-specific variance. It should be noted here that this method does not impose constraints on the spatial extent of the resulting long-distance connectivity. Thus different seeds can be connected to the same target regions, due to unique variance that distinguishes them from one another. In all resting-state connectivity analyses a voxelwise threshold of $p<0.005$ and a clusterwise threshold of $p<0.05$ (FDR corrected) were used.

Display

Slice views were generated using BrainVoyager QX (2.8.4, Brain Innovation, The Netherlands) from thresholded SPMs converted to VMP format using Neuroelf (1.0, http://neuroelf.net/) and overlaid on an MNI normalized anatomy converted to VMR format. Surface views were generated using CONN toolbox Surface display, which projects thresholded SPMs to a FreeSurfer surface registered to MNI space.

2.1.3. Results

Behavioral results

We first quantified the performance of the blind and sighted in all tasks.

Speech perception

The rate of miss (43.4%) and false-positive (6.5%) errors did not differ between the blind and the sighted ($t(26)=0.28$, $p=0.78$, and $t(26)=-0.19$, $p=0.85$, unpaired t-test).

Word generation

There was a significant effect of task ($F(2,21)=315.15$, $p<1.0e-5$, ANOVA). As expected, the Verb (1557 ms) and Initial (1840 ms) conditions were slower than the Repeat condition (1041 ms); and the Initial was slower than the Verb condition ($p<1.0e-5$ for all comparisons, paired t-test). There was no significant difference between groups ($F(1,21)=0.52$, $p=0.48$, ANOVA) and no task x group interaction ($F(2,21)=2.45$, $p=0.10$, ANOVA). Error rates followed the same pattern.

Executive control

There was a significant effect of task ($F(1,21)=36.38$, $p<1.0e-5$, ANOVA) and a task x group interaction ($F(1,21)=6.82$, $p=0.02$, ANOVA): The dual task was slower than the single task, and this difference was larger in the blind (mean: Dual 1543 ms, Single 1424 ms, $t(9)=4.33$, $p=0.002$, paired t-test) than in the sighted (mean: Dual 1422 ms, Single 1375 ms, $t(12)=3.98$, $p=0.002$, paired t-test). There was no overall difference between groups ($F(1,21)=2.5$, $p=0.13$, ANOVA). Error rates were low and showed no effect of group (mean: Blind 4%, Sighted 6.4%, $F(1,21)=0.81$, $p=0.37$, ANOVA). There was, however, an effect of condition ($F(1,21)=8.98$, $p=0.007$, ANOVA) where the Dual-task condition had a higher error rate than the Single-task condition (3.1% and 2.3%, respectively).

Long-term memory

Both groups performed well above chance with a mean d' value 1.46±0.41 (mean±std, $t(9)=11.14$, $p<1.0e-5$, one-sample t-test) in the blind and 1.00±0.66 in the sighted ($t(13)=5.644$, $p<1.0e-4$, one-sample t-test), with a non-significant trend to the advantage of the blind ($t(22)=1.92$, $p=0.068$, unpaired t-test).

Activations analysis

For each experiment and each contrast, we will present in turn the activations common to the sighted and the blind, and the activations which are larger in the blind than in the sighted, with an emphasis on visual cortex. Note that we found no activations larger in the sighted than in the blind. The separate results of the two groups may be found as supplemental material and will be referred to where relevant.

Speech perception

In both groups, the contrast of the four conditions (Sentences, Word-lists, Jabberwocky, Pseudo-word lists) minus rest activated bilateral primary and associative auditory areas in addition to bilateral inferior frontal sulcus (IFS), left inferior frontal gyrus (IFG) and bilateral medial superior frontal cortex (SFC; Fig. 1, bottom-left). Moreover, in the same contrast, there was stronger activation in the blind in bilateral visual cortex spanning its lateral, media and ventral aspects (Fig. 1, top-left; Supplementary Fig. 1 for separate group activations).

We assessed the main effect of semantics by contrasting (Sentences + Word-lists) minus (Jabberwocky + Pseudo-word lists) (Fig. 1, bottom-left; Supplementary Fig. 1). There was a left-predominant activation common to both groups along the bilateral superior temporal sulcus (STS). Stronger activation in the blind was found in the left anterior fusiform gyrus, overlapping with cytoarchitectonic areas FG1, 3 and 4 (area nomenclature follows the naming in SPM Anatomy toolbox; Eickhoff et al. 2005).

We then tested the main effect of syntax by contrasting (Sentences + Jabberwocky) minus (Word-lists + Pseudo-word lists). In the sighted, we found activations predominantly in the left STS and IFG (Supplementary Fig. 1). In the blind, however, the same regions were activated below significance threshold which is why we found no activation common to both groups. Also below significance was an activation in the left lingual gyrus when comparing the blind minus the sighted.

Due to the lack of a significant result in the main effect of syntax, we will only use the main effect of semantics in the following analysis and it will be referred to as the “Semantics” contrast.

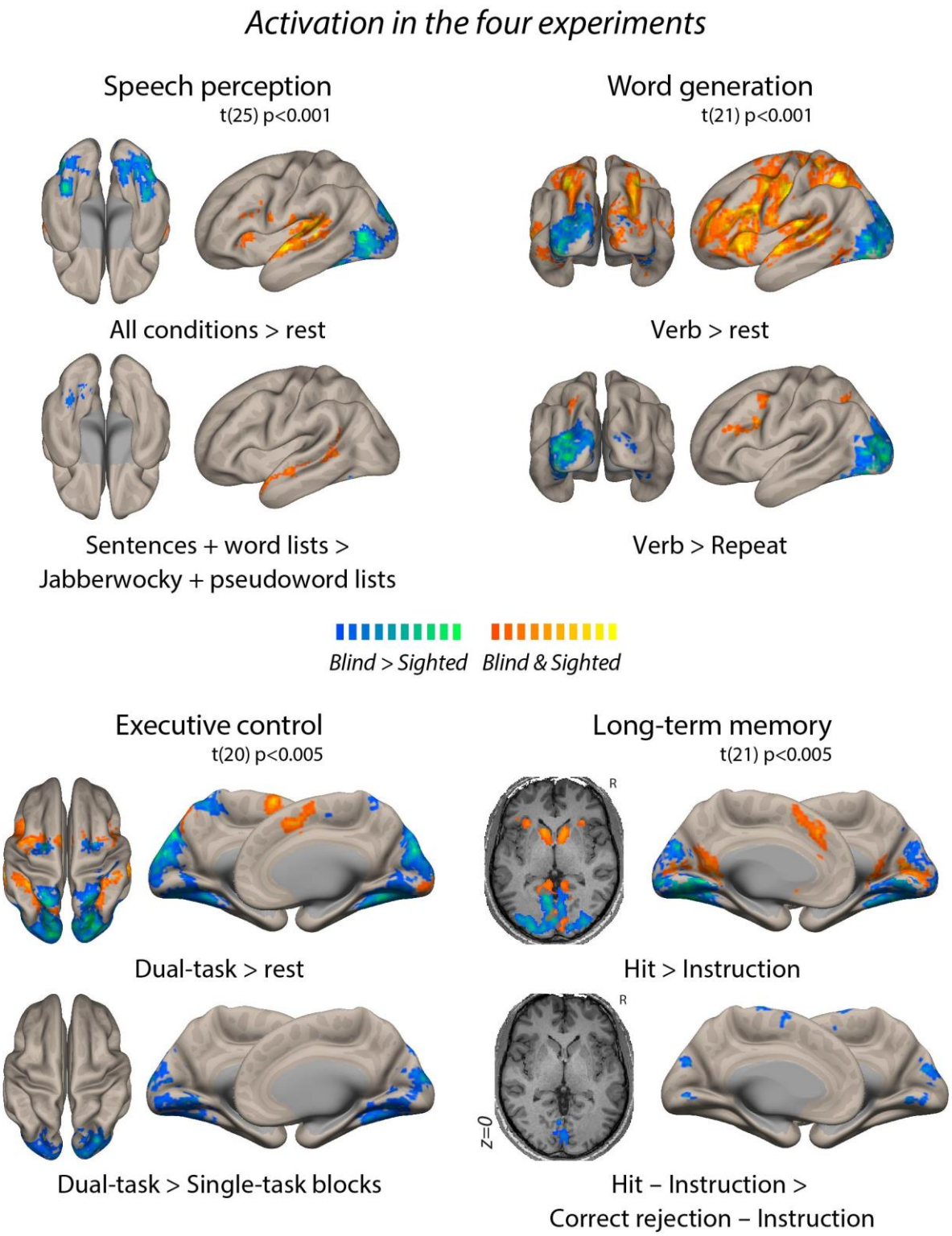


Figure 1 – Activation in the Blind and Sighted (conjunction and differences)

Surface and slice views of the whole-brain activation in selected conditions minus rest, and minus high-level control. For each contrast, hot colors show significant activation in the conjunction of blind and sighted, and cold colors show activation significantly stronger in the blind than in the sighted. There was no activation stronger in the sighted than

in the blind. With contrasts using high-level control conditions, all experiments activated the visual cortex in the blind relative to the sighted. Voxelwise thresholds are reported in the figure and all maps are clusterwise corrected ($p<0.05$).

Word generation

The contrast of the Verb minus Repeat conditions showed activation common to both groups in the left IFS and left-predominant medial SFC (Fig. 1, top-right). Activations were larger in the blind than in the sighted in left inferior and lateral occipital cortex and hOc2 on the medial face of the occipital cortex. In the right hemisphere, the differences were significant in the right ventral stream anterior to hOc3v (Fig. 1, top-left; Supplementary Fig. 1). The Initial minus Repeat contrast showed a very similar activation pattern to the Verb minus Repeat contrast (Supplementary Fig. 2). The comparisons between Initial and Verb conditions showed neither significant common activation nor significant group differences.

Since the Initial and the Verb conditions did not differ and considering that the Verb condition had been used in previous studies (Burton et al. 2002; Amedi et al. 2003; Ofan and Zohary 2007), it will represent verbal executive functions in the following analysis and be referred to as the "Generation" contrast.

Executive control

The Dual-task minus rest contrast showed bilateral activations common to both groups, encompassing the auditory (primary and associative), prefrontal (IFS, IFG), premotor, and medial SFC cortices in addition to the intra-parietal sulcus (IPS) and the frontal eye-fields (FEF; Fig. 1, top-right). Activations were stronger in the blind in bilateral inferior, lateral and medial occipital cortex extending to the posterior parietal cortex and to the superior parietal lobule, in addition to a region posterior to the FEF (Fig. 1, bottom-left; Supplementary Fig. 1).

The Dual-task minus Single-task contrast showed no activation common to both groups, due to a difference in lateralization of prefrontal activations between groups. Indeed in the sighted, the activation was located in the left anterior dorsolateral prefrontal cortex (DLPFC). In the blind, however, we found activations in the right DLPFC and right IPS in addition to a right-predominant occipital activation (Supplementary Fig. 1, top-right). Stronger activation was found bilaterally in the blind in a right-predominant region extending from the lateral occipital cortex to the posterior parietal cortex, in addition to parts of the right medial ventral stream (hOc4v and FG3), left posterior ventral stream (hOc4v, FG1), left lingual gyrus, and right medial occipital cortex (hOc2; Fig. 1, top-right).

The Dual-task minus Single-task contrast will be referred to as the "Executive Control" contrast in the following analysis.

Long-term memory

In both groups, a broad contrast sensitive to the memory task (Hit minus Instruction) activated the bilateral posterior cingulate cortex (PCC), heads of caudate, anterior insula, medial SFC, and primary visual cortex (hOc1; Fig. 1, bottom-right). Stronger activation in the blind was found in bilateral inferior, lateral and medial visual occipital cortex in addition to the right anterior IPS (Fig. 1, bottom-left; Supplementary Fig. 1).

We then used a more specific contrast of successful retrieval from episodic memory (Hits minus Correct rejections while subtracting the baseline Instruction condition; see Materials and Methods). This contrast showed no significantly activated clusters surviving the correction for multiple comparisons in the conjunction of both groups. However, clusters activated below extent threshold can be found in the right superior frontal gyrus (SFG), anterior cingulate cortex (ACC), right head of caudate, left angular gyrus and left cuneus (Table 2). All of which were previously shown to be implicated in memory retrieval (Spaniol et al. 2009). In the same contrast, sensitive to successful retrieval, stronger activation in the blind was found bilaterally in the medial occipital cortex overlapping with hOc1,2 and hOc3d (Fig. 1, bottom-left; Supplementary Fig. 1).

The successful retrieval contrast, representing the activation for long-term memory will be referred to as the “Long-term Memory” contrast in the following analysis.

Table 2 – Clusters activated below corrected extent threshold for the successful retrieval contrast in the conjunction of the blind and the sighted

Cluster location	Cluster size	Peak Z	Peak p(unc)	x,y,z {mm}
Superior prefrontal	28	3.71	0.000	48 35 20
Head of caudate	8	3.41	0.000	9 8 -1
Anterior cingulate cortex	31	3.30	0.000	-3 44 5
Cuneus	7	3.10	0.001	-6 -61 38
Angular	5	3.01	0.001	-45 -55 44

Functional connectivity analysis

In order to investigate the functional connectivity of the visual areas activated by our 4 cognitive paradigms, we used their respective contrasts of interest to define seed regions. For each of the “Semantics”, “Generation”, “Executive Control” and “Long-term Memory” contrasts, we defined as seed region the clusters which they activated in the visual cortex of the blind (Fig. 2). Those seed regions were then used in a functional connectivity analysis on resting-state data collected in the same subjects.

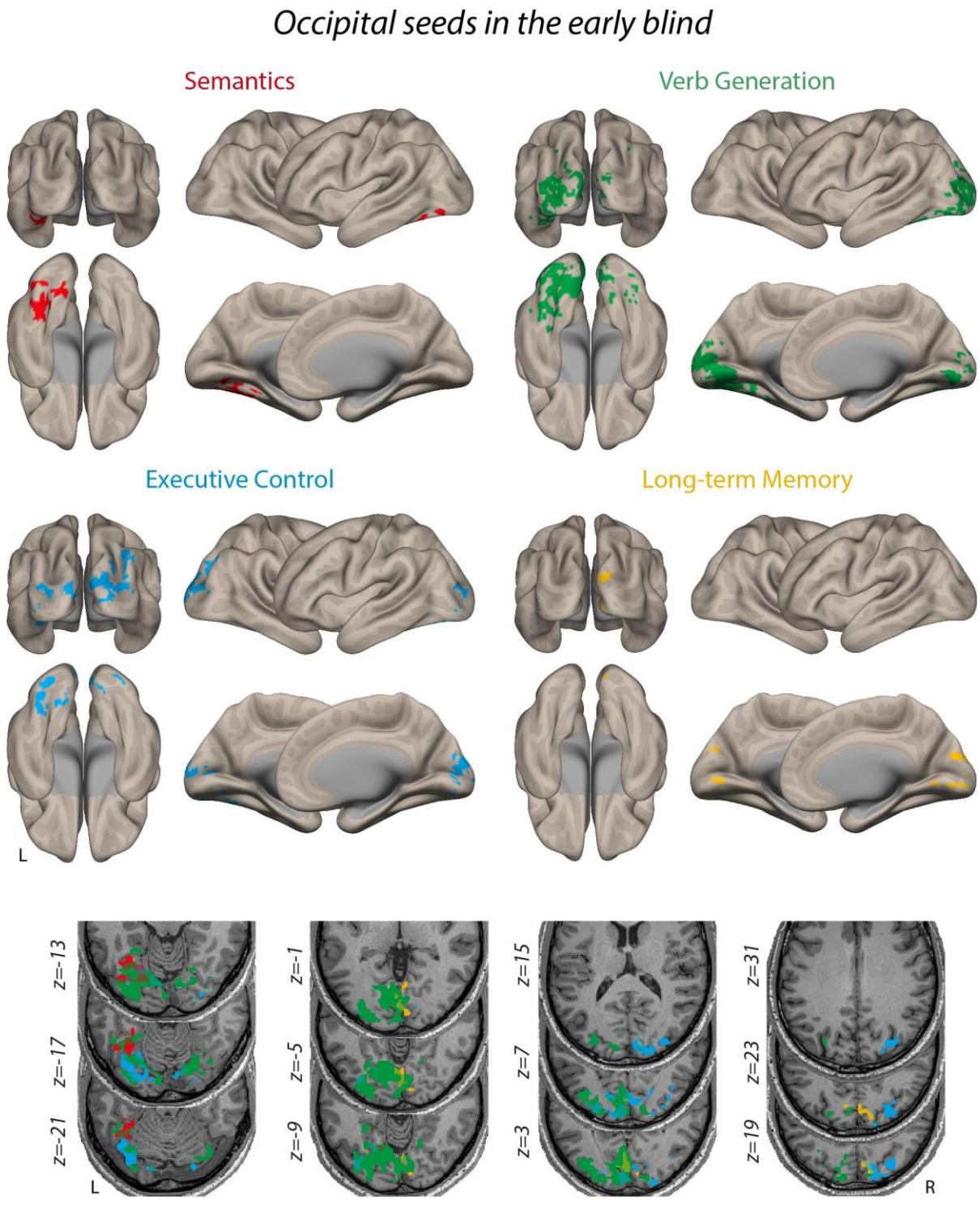


Figure 2 – Occipital seeds for the functional connectivity study

Surface and slice views of the activation by the four representative contrasts, in the visual cortex of the blind. Generation is shown in green, Executive Control in blue, Semantics in red and Long-term Memory in yellow. Those activations were used as seeds in the functional connectivity analysis.

We first computed the functional connectivity from those seeds using Pearson's correlation coefficient, and compared blind and sighted participants (Fig. 3). Overall, the 4 seed regions were more strongly connected to the auditory and somatosensory cortices in the sighted. Moreover, inter-hemispheric occipital connectivity was stronger in the sighted for the Generation, Executive Control and Semantics seeds. In the blind, all occipital seeds had stronger connectivity to the prefrontal and parietal cortices, while the Generation, Executive Control and Semantics seeds had also stronger connections to the temporal cortex.

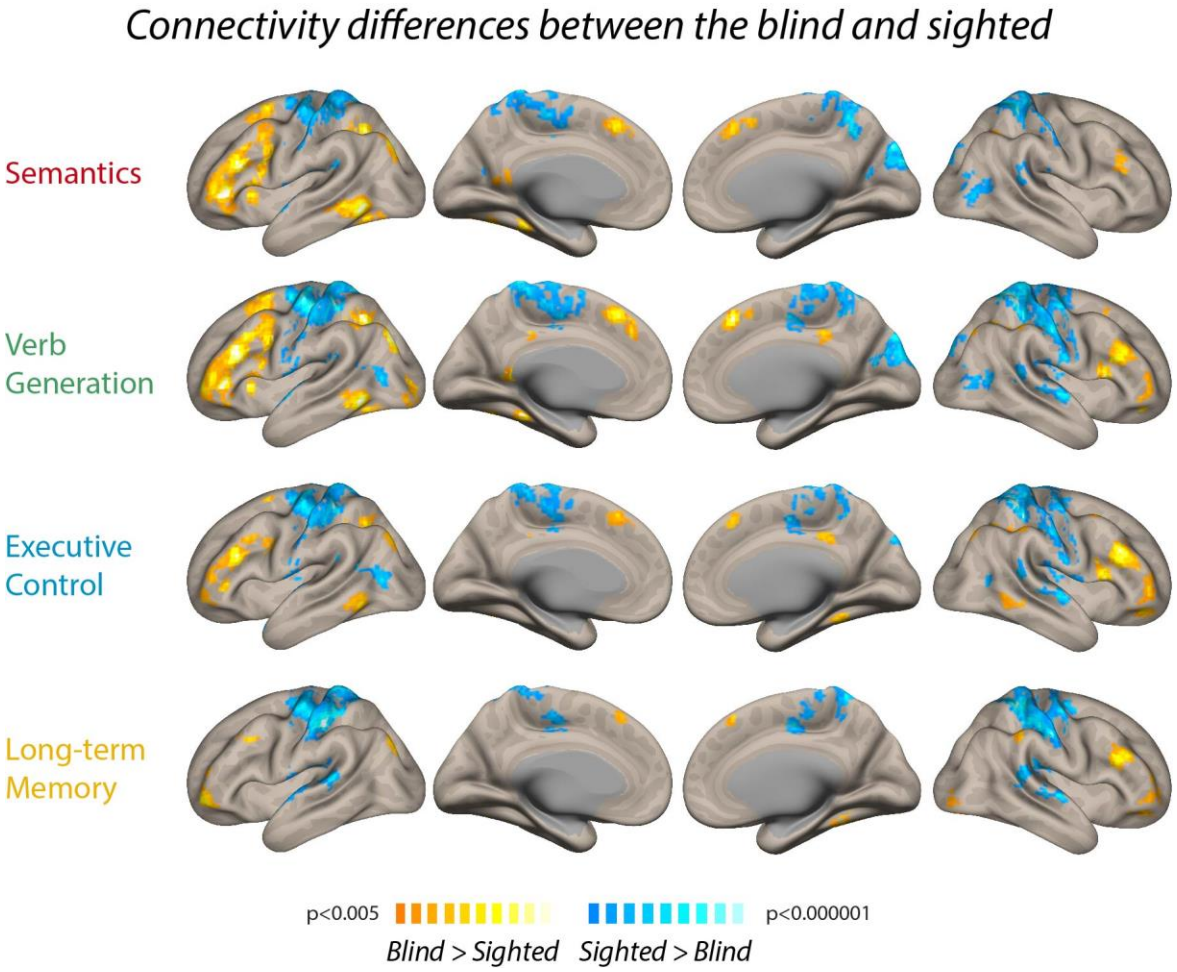


Figure 3 – Comparison of the functional connectivity between the blind and the sighted
Surface display of significant differences in functional connectivity between the blind and sighted, seeded from the 4 occipital regions, using Pearson's correlation coefficient. Hot colors show blind minus sighted differences, and cold colors show sighted minus blind differences. The voxelwise threshold was set to $p<0.005$ and all maps are clusterwise corrected ($p<0.05$).

In order to examine the unique connectivity of each seed region, i.e., that which is based only on non-shared signal, we used semi-partial correlations (see Materials and Methods; Fig. 4). In the blind group, the Generation seed was uniquely connected to the left middle and inferior frontal gyri corresponding to premotor cortex and Broca's area. The Semantics seed was uniquely connected to the left IFG just dorsal to the Generation cluster, and to the left lateral temporal cortex, from the occipitotemporal junction to the MTG/STS and the temporal pole. The Executive Control seed was uniquely connected to the right fronto-parietal executive network, in addition to the left IPS and right precuneus. The Long-term Memory seed was uniquely connected to a region in the right precuneus and the bilateral anterior cingulate cortex (ACC). The same analysis performed in the sighted showed an entirely different pattern than in the blind. As expected, unique connectivity was mostly present in the bilateral auditory and somatosensory cortices (regions with stronger connectivity to the visual cortex in the sighted). The Executive Control seed was uniquely connected to the parieto-occipital cortex. Moreover, no unique connectivity was observed in the prefrontal cortex (a region with weaker connectivity in the sighted) for any of the seed regions (**Supplementary** Fig. 3).

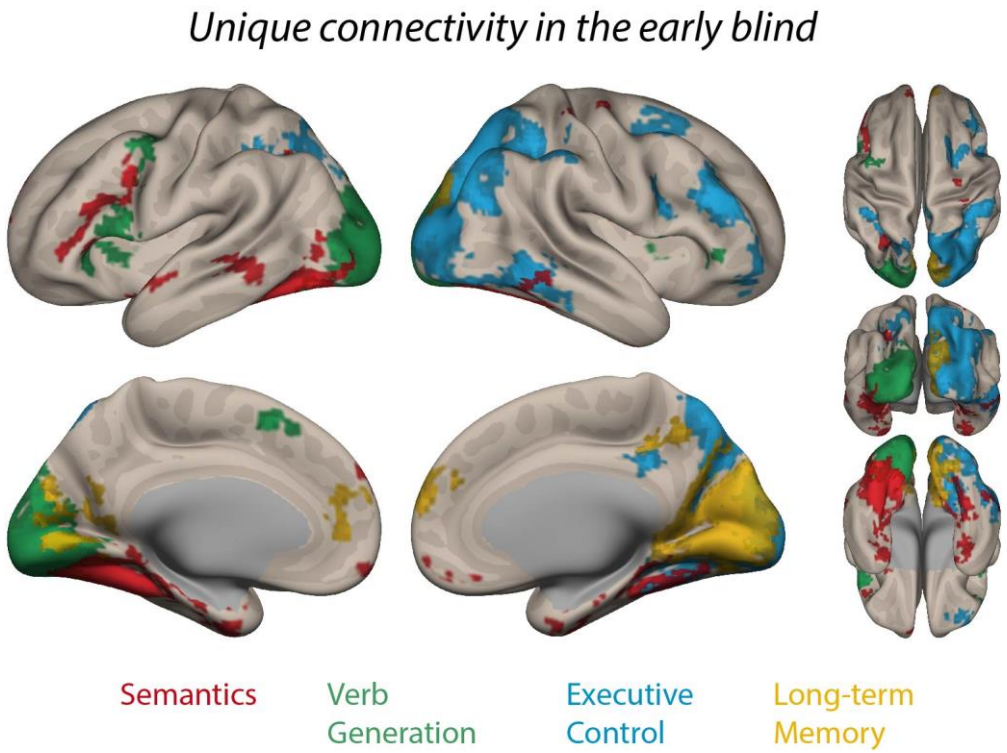


Figure 4 – Unique connectivity fingerprints of the occipital seeds in the blind
Surface view overlaying the unique connectivity fingerprint of the 4 occipital seeds, as delineated using semi-partial correlation. The voxelwise threshold was set to $p<0.005$ and all maps are clusterwise corrected ($p<0.05$).

2.1.4. Discussion

Using a combination of task and resting-state fMRI, we tested two predictions about the involvement of the visual cortex of the early blind in high-level cognitive functions. Each prediction will be discussed in turn, followed by addressing the links between our results and theories of brain reorganization under sensory deprivation. Unless stated otherwise, visual cortex will refer to the visual cortex of the blind.

Our first prediction was that high-level cognitive tasks should elicit activations in the visual cortex of the blind relative to sighted controls.

Non-perceptual activations in the visual cortex

All experiments showed that, relative to rest, non-perceptual tasks elicited activations in the visual cortex of the blind vs. sighted controls. Moreover, tighter contrasts controlling for low-level parameters demonstrated that those activations were actually related to high-level cognitive processes.

Speech perception

Our results agree with previous demonstrations that various aspects of language processing activate the visual cortex of the blind, including Braille reading (Sadato et al. 1996; Cohen et al. 1997; Beisteiner et al. 2015), word generation (Burton et al. 2002; Amedi et al. 2003; Watkins et al. 2012), speech perception (Bedny et al. 2011, 2015), semantic retrieval (Noppeney et al. 2003) and sentence-level syntax and semantics (Röder et al. 2002; Lane et al. 2015). Using a design similar to ours, Bedny et al. (2011) found sensitivity to semantics, but also to syntax, for which we only found sub-threshold activation. Sensitivity to syntax, as well as more extensive activations, may result from their use of a demanding working-memory task, while we chose a shallower perceptual task, in order to equate attentional engagement across conditions.

Word generation

The word generation task involves both language and executive functions and activates a large part of the visual cortex with strong left predominance, as it has been shown using auditory or Braille words (Burton et al. 2002; Amedi et al. 2003; Ofan and Zohary 2007; Struiksma et al. 2011; Watkins et al. 2012). As the task included a verbal semantic component, activations included left ventral cortex, similar to the Semantic contrast. Moreover, they extended to left-predominant lateral occipital areas which may be involved in the executive component. Indeed those left lateral areas were roughly symmetrical to those activated in the right hemisphere by the non-verbal executive task, to be discussed next.

Executive control

Occipital activation by blocks requiring task-switching indicates involvement of the visual cortex in executive task-set reconfiguration (Monsell 2003), typically a dorsolateral prefrontal function (Koechlin et al. 2003). This novel finding fits with the increased resting-state connectivity observed in the blind between visual and prefrontal regions (Liu et al. 2007; Burton et al. 2014). Previous studies of executive control in the blind targeted working memory. Using tactile stimulation, Burton et al. (2010) found no evidence of the visual cortex contributing to working memory (Burton et al. 2010). However, (Deen et al. 2015) combining fMRI activation and functional connectivity provided indirect evidence that the visual cortex is involved in auditory working memory. Note that a wide variety of tasks recruit executive processes, and due to the lack of stringent control conditions, some of the visual activations observed in early studies of language and memory (Sadato et al. 1996; Burton et al. 2002; Amedi et al. 2003) may be accounted for by executive cost (Lewis et al. 2010; Park et al. 2011).To the best of our knowledge, this is the first study directly showing the recruitment of non-verbal executive control in the blind. This does not, however, rule out that the right lateral visual cortex might intervene in other cognitive functions such as spatial attention and numerical processing (Collignon et al. 2011; Kanjlia et al. 2016).

Long-term memory

The mesial visual cortex was activated during successful retrieval in an incidental long-term memory task (i.e. for hits over correct rejections). Those activations overlap with the bilateral activations observed when EB recall a list of abstract words (Amedi et al. 2003) or perform an old/new judgment (Raz et al. 2005). Both studies support a causal involvement of the visual cortex in memory retrieval by showing a correlation between activation level and individual performance. Using both auditory and Braille words, Burton et al. (2012) showed that such memory-related activations occur irrespective of input modality, but with no advantage for successful retrieval (Burton et al. 2012).

Some voxels were found to be overlapping between several contrasts (Fig. 2). Most notable is the overlap between the Verb Generation and the other 3 contrasts, which may arise due to overlapping cognitive functions. Indeed, the Verb minus Repeat contrast encompasses cognitive processes related to semantic access, retrieval from memory and executive control. In addition, it is possible that spatial blurring due to averaging across subjects contributes to creating such overlaps.

In summary, we found that all tested cognitive processes activate the visual cortex in the blind. Moreover, as we used task-specific high-level controls, we may conclude that visual activations reflect distinct cognitive processes related to memory, language and executive processing.

We now discuss our second prediction, i.e., that visual areas activated under those paradigms are connected to distinct functional networks reflecting their novel functional role.

Integration in brain-scale functional networks

In agreement with previous studies, we found that, in the blind, visual seeds generally showed (1) a reduced inter-hemispheric connectivity with contralateral regions; (2) a reduced connectivity with auditory, somatosensory and motor areas; and (3) an increased connectivity with associative cortex in the lateral prefrontal, superior parietal, and mid-temporal areas (Liu et al. 2007; Yu et al. 2008; Bedny et al. 2011; Watkins et al. 2012; Butt et al. 2013; Qin et al. 2013; Burton et al. 2014; Wang et al. 2014; Deen et al. 2015; see however Heine et al. 2015). The increased connectivity to what resembles a general executive network likely reflects the involvement of the visual cortex in higher cognition.

Beyond such commonalities, we were mostly interested in the unique connectivity of each seed region, which we isolated using semi-partial correlation. Confirming our prediction, in the blind only, visual seed regions showed unique connectivity with distant task-related networks. First, language-related seeds, derived from the Semantics and Generation contrasts, were connected to core language areas, i.e., Broca's area and the left lateral and anterior temporal lobe, both consistently involved in verbal semantics (Patterson et al. 2007; Binder and Desai 2011). In agreement with this result, Bedny et al. (2011) using seed-based functional connectivity and (Watkins et al. 2012) using ICA decomposition showed visual cortex connectivity with parts of the language network. Moreover, Kanjlia et al. (2016) showed that this fronto-occipital connectivity is specific to language over mathematics. Second, the non-verbal Executive Control seed was mainly connected to a right-hemispheric frontoparietal executive network. In general, task switching activates bilateral frontoparietal areas (Kim et al. 2012). The present right-lateralization may result from the use of non-verbal material (Yeung et al. 2006; Geddes et al. 2014) but also from the reduced interhemispheric correlation in the visual cortex of the blind. The decoupling of the left and right visual cortices may reflect their recycling by different cognitive functions, implying distinct and asymmetric connectivity patterns. In agreement with this hypothesis, in the sighted, the connectivity of three out of the four visual seeds was symmetrical (Supplementary Fig. 3). Last, the Long-term Memory seed was uniquely connected to the precuneus and the bilateral medial prefrontal cortex, which are consistently involved in episodic memory retrieval, particularly in a contrast of recollection vs. familiarity (Spaniol et al. 2009; Kim 2010). Note that the use of semi-partial correlation isolates only what is uniquely connected to each seed. Therefore, partial overlap between seed regions is considered as shared signal that is regressed out from both seeds. Any connectivity contributed by those overlapping regions is invisible to this analysis.

Previous studies dealing with the relationship between the activation and connectivity of the visual cortex in the early blind had demonstrated that frontal regions with increased connectivity to the visual cortex could either be sensitive to language or working-memory load (Deen et al. 2015). In addition, visual regions activated by language and mathematics are preferentially connected to long-distance regions processing language and mathematics, respectively (Kanjlia et al. 2016). Our results generalize this relationship between visual cortex activation and functional connectivity to a larger set of cognitive functions. Those include non-verbal executive processes, which were never directly tested in the blind before, and long-term memory. Moreover, having a large set of tasks and using the unique connectivity of their activated areas permit a more precise description of the visual cortex reorganization in the early blind.

General discussion

How do our results relate to general accounts of cortical plasticity in the blind? Activations of the visual cortex by non-visual stimuli may correspond to various perceptual (e.g. motion) and non-perceptual (e.g. memory) processes. According to the metamodal/supramodal approach, the same perceptual computations may be performed in the so-called visual cortex irrespective of input modality (Pascual-Leone and Hamilton 2001; Pietrini et al. 2004), accounting for the involvement of the visual cortex of the blind in non-visual perception (Cecchetti et al. 2016). Metamodality, however, cannot explain the drastic change from low-level visual processing to high-level non-perceptual computations that the visual cortex undergoes in blindness, a phenomenon often termed crossmodal plasticity (Rauschecker 1995; Renier et al. 2014).

It has been recently hypothesized that such recycling of deafferented visual cortex is driven and shaped during development by pre-existing anatomical connections to frontal, parietal and temporal areas (Bedny 2017). That our results are in line with such a connectivity-based account is clearest in the case of the left ventral language-related seeds (Semantics and Generation), which overlap with the Visual Word Form Area. This region is involved in written words recognition in literate subjects, and has privileged anatomical connections to language areas in literate adults (Bouhali et al. 2014), but also in children before reading acquisition (Saygin et al. 2016). Similarly, the Executive Control and Generation seeds extend into lateral occipital cortex, which has direct anatomical connections to prefrontal regions through the IFOF and SLF (Forkel et al. 2014). Finally, the cingulum may connect the occipital Long-term Memory seed to mesial frontal and parietal regions with which it establishes novel functional links in the blind (Catani et al. 2002), although the existence of occipital cingulum fibers is still disputed (Rojkova et

al. 2016). Notwithstanding, the apparent coexistence of this recycling and of the persistent retinotopic arrangement of the visual cortex in the early blind (Striem-Amit et al. 2015) remains an open question.

In conclusion, using a broad set of language, memory, and executive tasks within the same blind subjects, we demonstrate the selective integration of different patches of the visual cortex into brain-scale networks with distinct topography, lateralization, and functional roles. Identifying the informational content and casual role of those occipital activations will be the main future challenge.

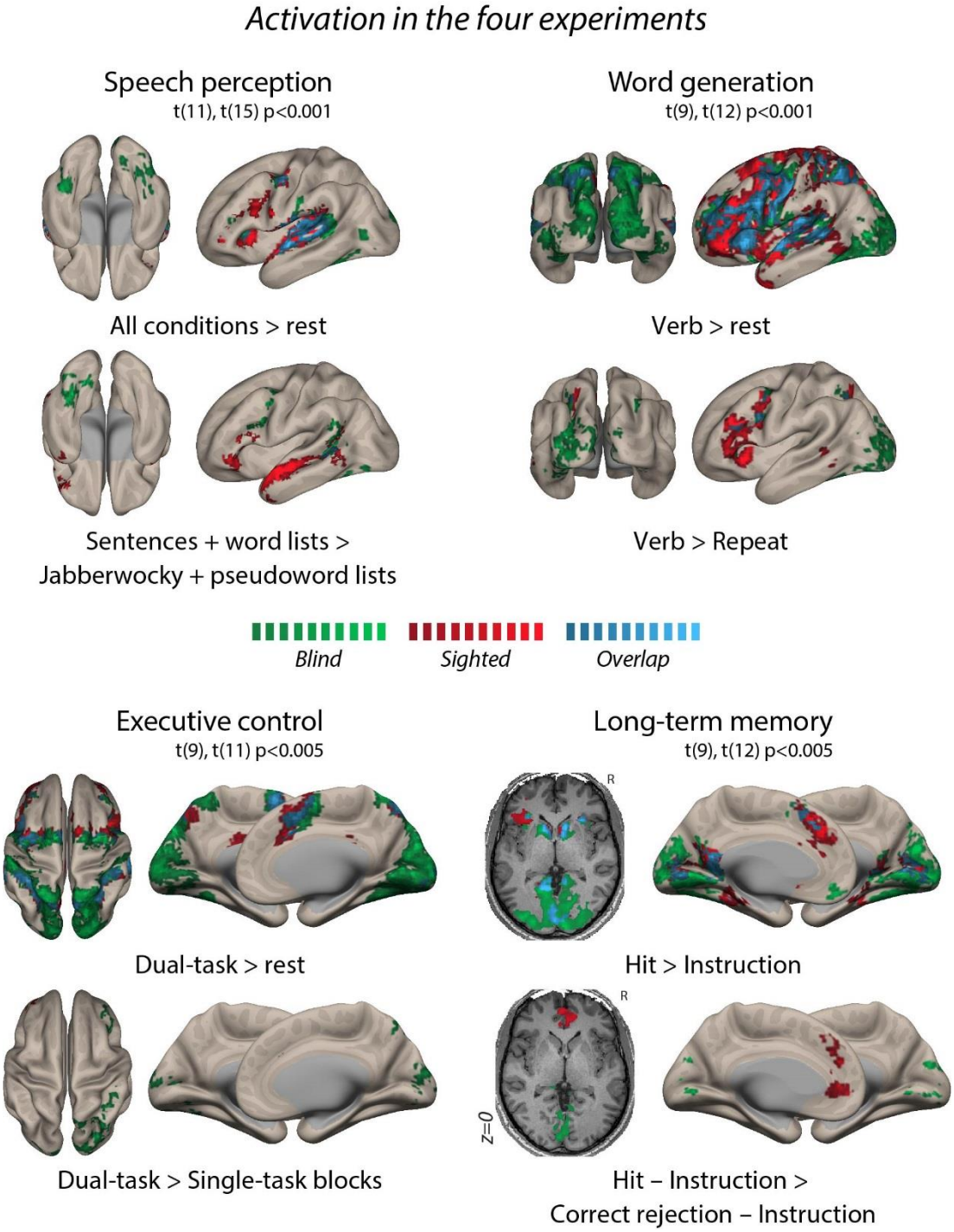
Funding

This work was supported by the “Investissements d’avenir” program of the French National Research Agency (ANR-10-IAIHU-06) to the Brain and Spine Institute, the LABEX LIFESENSES project of the French National Research Agency (ANR-10-LABX-65) to the Vision Institute and the “Leshanot Chaim” Foundation (to SA).

Acknowledgments

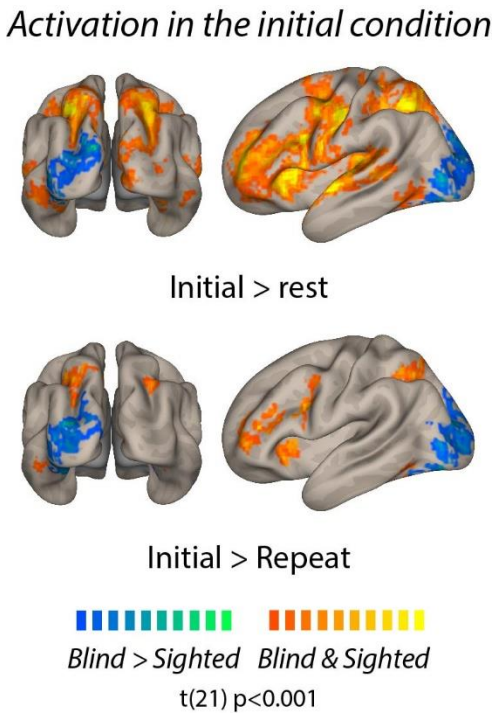
The authors would like to thank A. Marchand for coordinating the data acquisition and S. Mohand-Said for the help in recruiting subjects.

2.1.5. Supplementary information



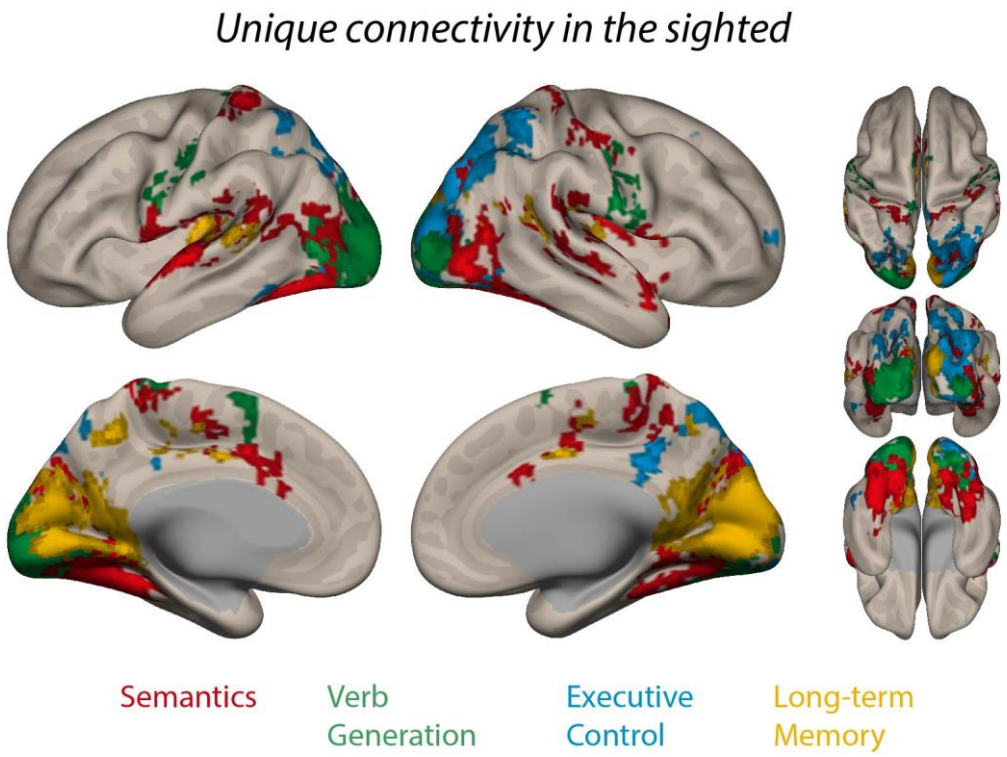
Supplementary Figure 1 – Activation in the Blind and Sighted (separately)

Surface and slice views of whole-brain activation in selected conditions minus rest and, minus high-level control. For each contrast, shades of green show significant activations in the blind, and shades of red show significant activations in the sighted (overlaying voxels are displayed in shades of blue for visualization purposes). Voxelwise thresholds are reported in the figure and all maps are clusterwise corrected ($p<0.05$).



Supplementary Figure 2 – Activation in the Blind and Sighted for the Initial condition (conjunction and differences).

Surface views of the whole-brain activation in the Initial condition minus rest, and minus high-level control. For each contrast, hot colors show significant activations in the conjunction of blind and sighted, and cold colors show activation significantly stronger in the blind than in the sighted. There was no activation stronger in the sighted than in the blind. Voxelwise thresholds are reported in the figure and all maps are clusterwise corrected ($p<0.05$).



Supplementary Figure 3 – Unique connectivity fingerprints for the occipital seeds in the sighted.
Surface view overlaying the unique connectivity fingerprint of the 4 occipital seeds, as delineated using semi-partial correlation. The voxelwise threshold was set to $p<0.005$ and all maps are clusterwise corrected ($p<0.05$).

2.1.6. References

Amedi A, Floel A, Knecht S, Zohary E, Cohen LG. 2004. Transcranial magnetic stimulation of the occipital pole interferes with verbal processing in blind subjects. Nat Neurosci. 7:1266–1270.

Amedi A, Raz N, Pianka P, Malach R, Zohary E. 2003. Early "visual" cortex activation correlates with superior verbal memory performance in the blind. Nat Neurosci. 6:758–766.

Bedny M. 2017. Evidence from Blindness for a Cognitively Pluripotent Cortex. Trends Cogn Sci. 21:637–648.

Bedny M, Pascual-Leone A, Dodell-Feder D, Fedorenko E, Saxe R. 2011. Language processing in the occipital cortex of congenitally blind adults. Proc Natl Acad Sci. 108:4429–4434.

Bedny M, Richardson H, Saxe R. 2015. "Visual" Cortex Responds to Spoken Language in Blind Children. J Neurosci Off J Soc Neurosci. 35:11674–11681.

Behzadi Y, Restom K, Liau J, Liu TT. 2007. A component based noise correction method (CompCor) for BOLD and perfusion based fMRI. NeuroImage. 37:90–101.

Beisteiner R, Windischberger C, Geißler A, Gartus A, Uhl F, Moser E, Deecke L, Lanzenberger R. 2015. FMRI correlates of different components of Braille reading by the blind. Neurol Psychiatry Brain Res. 21:137–145.

Binder JR, Desai RH. 2011. The neurobiology of semantic memory. Trends Cogn Sci. 15:527–536.

Bouhali F, Thiebaut de Schotten M, Pinel P, Poupon C, Mangin J-F, Dehaene S, Cohen L. 2014. Anatomical connections of the visual word form area. J Neurosci Off J Soc Neurosci. 34:15402–15414.

Brainard DH. 1997. The Psychophysics Toolbox. Spat Vis. 10:433–436.

Burton H, Sinclair RJ, Agato A. 2012. Recognition memory for Braille or spoken words: an fMRI study in early blind. Brain Res. 1438:22–34.

Burton H, Sinclair RJ, Dixit S. 2010. Working memory for vibrotactile frequencies: comparison of cortical activity in blind and sighted individuals. Hum Brain Mapp. 31:1686–1701.

Burton H, Snyder AZ, Diamond JB, Raichle ME. 2002. Adaptive changes in early and late blind: a FMRI study of verb generation to heard nouns. J Neurophysiol. 88:3359–3371.

Burton H, Snyder AZ, Raichle ME. 2014. Resting state functional connectivity in early blind humans. Front Syst Neurosci. 8.

Butt OH, Benson NC, Datta R, Aguirre GK. 2013. The fine-scale functional correlation of striate cortex in sighted and blind people. J Neurosci Off J Soc Neurosci. 33:16209–16219.

Catani M, Howard RJ, Pajevic S, Jones DK. 2002. Virtual in Vivo Interactive Dissection of White Matter Fasciculi in the Human Brain. NeuroImage. 17:77–94.

Cecchetti L, Kupers R, Ptito M, Pietrini P, Ricciardi E. 2016. Are Supramodality and Cross-Modal Plasticity the Yin and Yang of Brain Development? From Blindness to Rehabilitation. Front Syst Neurosci. 10:89.

Cohen LG, Celnik P, Pascual-Leone A, Corwell B, Falz L, Dambrosia J, Honda M, Sadato N, Gerloff C, Catalá MD, Hallett M. 1997. Functional relevance of cross-modal plasticity in blind humans. Nature. 389:180–183.

Collignon O, Vandewalle G, Voss P, Albouy G, Charbonneau G, Lassonde M, Lepore F. 2011. Functional specialization for auditory-spatial processing in the occipital cortex of congenitally blind humans. Proc Natl Acad Sci. 108:4435–4440.

Cox RW, Chen G, Glen DR, Reynolds RC, Taylor PA. 2017. fMRI clustering and false-positive rates. Proc Natl Acad Sci. 114:E3370–E3371.

Deen B, Saxe R, Bedny M. 2015. Occipital cortex of blind individuals is functionally coupled with executive control areas of frontal cortex. J Cogn Neurosci. 27:1633–1647.

Eickhoff SB, Stephan KE, Mohlberg H, Grefkes C, Fink GR, Amunts K, Zilles K. 2005. A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data. NeuroImage. 25:1325–1335.

Forkel SJ, Thiebaut de Schotten M, Kawadler JM, Dell'Acqua F, Danek A, Catani M. 2014. The anatomy of fronto-occipital connections from early blunt dissections to contemporary tractography. Cortex. 56:73–84.

Fox MD, Raichle ME. 2007. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nat Rev Neurosci. 8:700–711.

Geddes MR, Tsuchida A, Ashley V, Swick D, Fellows LK. 2014. Material-specific interference control is dissociable and lateralized in human prefrontal cortex. Neuropsychologia. 64:310–319.

Gougoux F, Zatorre RJ, Lassonde M, Voss P, Lepore F. 2005. A functional neuroimaging study of sound localization: visual cortex activity predicts performance in early-blind individuals. PLoS Biol. 3:e27.

Hamilton R, Keenan JP, Catala M, Pascual-Leone A. 2000. Alexia for Braille following bilateral occipital stroke in an early blind woman. Neuroreport. 11:237–240.

Heine L, Bahri MA, Cavaliere C, Soddu A, Laureys S, Ptito M, Kupers R. 2015. Prevalence of increases in functional connectivity in visual, somatosensory and language areas in congenital blindness. Front Neuroanat. 9:86.

Kanjlia S, Lane C, Feigenson L, Bedny M. 2016. Absence of visual experience modifies the neural basis of numerical thinking. Proc Natl Acad Sci. 113:11172–11177.

Kim C, Cilles SE, Johnson NF, Gold BT. 2012. Domain general and domain preferential brain regions associated with different types of task switching: A Meta-Analysis. Hum Brain Mapp. 33:130–142.

Kim H. 2010. Dissociating the roles of the default-mode, dorsal, and ventral networks in episodic memory retrieval. NeuroImage. 50:1648–1657.

Kleiner M, Brainard D, Pelli D, Ingling A, Murray R, Broussard C, others. 2007. What's new in Psychtoolbox-3. Perception. 36:1.

Koechlin E, Ody C, Kouneiher F. 2003. The architecture of cognitive control in the human prefrontal cortex. Science. 302:1181–1185.

Konishi S, Wheeler ME, Donaldson DI, Buckner RL. 2000. Neural Correlates of Episodic Retrieval Success. NeuroImage. 12:276–286.

Lane C, Kanjlia S, Omaki A, Bedny M. 2015. "Visual" Cortex of Congenitally Blind Adults Responds to Syntactic Movement. J Neurosci Off J Soc Neurosci. 35:12859–12868.

Lewis LB, Saenz M, Fine I. 2010. Mechanisms of cross-modal plasticity in early-blind subjects. J Neurophysiol. 104:2995–3008.

Liu Y, Yu C, Liang M, Li J, Tian L, Zhou Y, Qin W, Li K, Jiang T. 2007. Whole brain functional connectivity in the early blind. Brain J Neurol. 130:2085–2096.

Monsell S. 2003. Task switching. Trends Cogn Sci. 7:134–140.

Murray MM, Thelen A, Thut G, Romei V, Martuzzi R, Matusz PJ. 2016. The multisensory function of the human primary visual cortex. Neuropsychologia. 83:161–169.

New B, Pallier C, Brysbaert M, Ferrand L. 2004. Lexique 2: a new French lexical database. Behav Res Methods Instrum Comput J Psychon Soc Inc. 36:516–524.

Noppeney U, Friston KJ, Price CJ. 2003. Effects of visual deprivation on the organization of the semantic system. Brain J Neurol. 126:1620–1627.

Ofan RH, Zohary E. 2007. Visual cortex activation in bilingual blind individuals during use of native and second language. Cereb Cortex N Y N 1991. 17:1249–1259.

Park H-J, Chun J-W, Park B, Park H, Kim JI, Lee JD, Kim J-J. 2011. Activation of the occipital cortex and deactivation of the default mode network during working memory in the early blind. J Int Neuropsychol Soc JINS. 17:407–422.

Pascual-Leone A, Hamilton R. 2001. The metamodal organization of the brain. Prog Brain Res. 134:427–445.

Patterson K, Nestor PJ, Rogers TT. 2007. Where do you know what you know? The representation of semantic knowledge in the human brain. Nat Rev Neurosci. 8:976–987.

Pelli DG. 1997. The VideoToolbox software for visual psychophysics: transforming numbers into movies. Spat Vis. 10:437–442.

Pietrini P, Furey ML, Ricciardi E, Gobbini MI, Wu W-HC, Cohen L, Guazzelli M, Haxby JV. 2004. Beyond sensory images: Object-based representation in the human ventral pathway. Proc Natl Acad Sci U S A. 101:5658–5663.

Qin W, Liu Y, Jiang T, Yu C. 2013. The development of visual areas depends differently on visual experience. PloS One. 8:e53784.

Rauschecker JP. 1995. Compensatory plasticity and sensory substitution in the cerebral cortex. Trends Neurosci. 18:36–43.

Raz N, Amedi A, Zohary E. 2005. V1 Activation in Congenitally Blind Humans is Associated with Episodic Retrieval. Cereb Cortex. 15:1459–1468.

Renier L, De Volder AG, Rauschecker JP. 2014. Cortical plasticity and preserved function in early blindness. Neurosci Biobehav Rev. 41:53–63.

Ricciardi E, Bonino D, Pellegrini S, Pietrini P. 2014. Mind the blind brain to understand the sighted one! Is there a supramodal cortical functional architecture? Neurosci Biobehav Rev. 41:64–77.

Röder B, Stock O, Bien S, Neville H, Rösler F. 2002. Speech processing activates visual cortex in congenitally blind humans. Eur J Neurosci. 16:930–936.

Rojkova K, Volle E, Urbanski M, Humbert F, Dell'Acqua F, Thiebaut de Schotten M. 2016. Atlasing the frontal lobe connections and their variability due to age and education: a spherical deconvolution tractography study. Brain Struct Funct. 221:1751–1766.

Rugg MD, Henson RN. 2002. Episodic memory retrieval: an (event-related) functional neuroimaging perspective. Cogn Neurosci Mem Encoding Retr. 3–37.

Sadato N, Pascual-Leone A, Grafman J, Ibañez V, Deiber MP, Dold G, Hallett M. 1996. Activation of the primary visual cortex by Braille reading in blind subjects. Nature. 380:526–528.

Saygin ZM, Osher DE, Norton ES, Youssoufian DA, Beach SD, Feather J, Gaab N, Gabrieli JDE, Kanwisher N. 2016. Connectivity precedes function in the development of the visual word form area. Nat Neurosci. 19:1250–1255.

Spaniol J, Davidson PSR, Kim ASN, Han H, Moscovitch M, Grady CL. 2009. Event-related fMRI studies of episodic encoding and retrieval: Meta-analyses using activation likelihood estimation. Neuropsychologia. 47:1765–1779.

Striem-Amit E, Ovadia-Caro S, Caramazza A, Margulies DS, Villringer A, Amedi A. 2015. Functional connectivity of visual cortex in the blind follows retinotopic organization principles. Brain J Neurol. 138:1679–1695.

Struiksma ME, Noordzij ML, Neggers SFW, Bosker WM, Postma A. 2011. Spatial language processing in the blind: evidence for a supramodal representation and cortical reorganization. PloS One. 6:e24253.

Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, Mazoyer B, Joliot M. 2002. Automated Anatomical Labeling of Activations in SPM Using a Macroscopic Anatomical Parcellation of the MNI MRI Single-Subject Brain. NeuroImage. 15:273–289.

Van Dijk KRA, Sabuncu MR, Buckner RL. 2012. The influence of head motion on intrinsic functional connectivity MRI. NeuroImage. 59:431–438.

Wang D, Qin W, Liu Y, Zhang Y, Jiang T, Yu C. 2014. Altered resting-state network connectivity in congenital blind. Hum Brain Mapp. 35:2573–2581.

Watkins KE, Cowey A, Alexander I, Filippini N, Kennedy JM, Smith SM, Ragge N, Bridge H. 2012. Language networks in anophthalmia: maintained hierarchy of processing in "visual" cortex. Brain J Neurol. 135:1566–1577.

Whitfield-Gabrieli S, Nieto-Castanon A. 2012. Conn: a functional connectivity toolbox for correlated and anticorrelated brain networks. Brain Connect. 2:125–141.

Yeung N, Nystrom LE, Aronson JA, Cohen JD. 2006. Between-task competition and cognitive control in task switching. J Neurosci Off J Soc Neurosci. 26:1429–1438.

Yu C, Liu Y, Li J, Zhou Y, Wang K, Tian L, Qin W, Jiang T, Li K. 2008. Altered functional connectivity of primary visual cortex in early blindness. Hum Brain Mapp. 29:533–543.

2.2. Innate connectivity of visual cortex

In the previous section, we demonstrated that there is a correspondence between activation and connectivity in the blind visual cortex. More specifically, we showed that: regions activated in word generation were uniquely connected to the dorsolateral prefrontal cortex; regions sensitive to the semantic contrast of speech perception were uniquely connected to the left lateral temporal cortex and inferior frontal cortex; regions sensitive to the executive cost of task-switching were connected to the right fronto-parietal executive network; and last, regions activated during retrieval from memory were connected to the right precuneus and the bilateral anterior cingulate cortex (ACC). In contrast, these regions are mainly uniquely connected to the somatosensory and auditory cortices in the sighted, with the exception of the dorsal occipital seed defined using the executive control contrast that is connected to the posterior part of the intraparietal sulci.

Those results are in line with the proposition that visual cortex deafferented from its visual inputs is driven and shaped during development by pre-existing anatomical connections to frontal, parietal and temporal areas (Bedny 2017). However, our findings only reveal the result of a long developmental process. They cannot not say much about the early state of the system and the influence of innate connections on its development.

At the heart of innate connectivity theories lies the speculation that either pre-existing anatomical connections to frontal, parietal and temporal areas become more dominant or transient long-range connections are stabilized during development without visual input (Bavelier and Neville 2002; Bedny 2017). We therefore probed the visual cortex in close proximity to birth in order to look for evidence supporting the existence of such connections that would disappear in sighted adults due to pruning or the dominance of visual input. Hence, beyond the expected resemblance between sighted neonates and adults, finding additional resemblance between blind adults and sighted neonates would reinforce the idea that pre-existing connectivity underlies the acquisition of novel functions by the blind visual cortex.

2.2.1. Hypothesis and analysis

More formally, we hypothesized that equivalent visual regions in blind adults and sighted full-term neonates may show similar long-distance connectivity that does not survive in sighted adults. To test this hypothesis, we used a dataset of 37 neonates from the Developing Human Connectome Project (dHCP; Hughes et al. 2017). The dataset includes high-resolution anatomical images and a resting-state functional MRI acquisition during natural sleep (acquisition details, preprocessing steps and analysis described in Section 2.2.4). A straightforward way to test the innate connectivity hypothesis would be to

repeat the functional connectivity analysis conducted in blind and sighted adults using the neonate dataset. For that, seed regions defined from the activation maps of the four contrasts of interest would need to be transformed to "neonate-space", an anatomical space representing a neonate at the gestational age of 40 weeks (Serag et al. 2012). However, since adult and neonate brains differ substantially in morphology, a simple adult-to-neonate transformation cannot be trivially conceived. For example, distance between an anatomical point in the inferior temporal cortex and the occipital pole will not vary simply according to the brain size ratio between adults and neonates due to different maturation trajectories. Therefore, we chose to generate seed regions for neonates using anatomical landmarks. First, we identified the anatomical landmark at the activation peak of each contrast of interest (cognitive function) in the blind (Table 2.2.1). Then, we defined a (3mm radius) sphere centered on the equivalent anatomical landmark in neonates, which we used as a seed region in the neonates. In the particular case of the verb generation contrast, we chose to use two activation peaks for, one ventral and one dorsal, because this contrast induces wide-spread activations in the visual cortex and involves more than one cognitive function.

Table 2.2.1 – Seed regions for neonate functional connectivity analysis

Cognitive function	Anatomical landmark	Hemisphere	MNI coordinates
Semantics	Posterior fusiform gyrus	Left	-33, -58, -19
Verb generation – dorsal	Middle occipital gyrus	Left	-27, -88, 11
Verb generation – ventral	Calcarine sulcus (middle region)	Left	-12, -79, -1
Executive control	Superior occipital gyrus	Right	30, -82, 20
Long-term memory	Cuneus (dorsal V2)	Right	12, -88, 20

2.2.2. Results

In order to examine of the unique connectivity of each seed region, i.e., that which is based only on non-shared signal between regions, connectivity was assessed using semi-partial correlations, as in the adult analysis. In the neonates, the Semantics seed was uniquely connected to left lateral posterior temporal cortex, to the whole extent of left superior temporal gyrus and to the left angular gyrus (Figure 2.2.1 a). The dorsal seed of verb generation, residing in the left middle occipital gyrus, was uniquely connected to the left intraparietal sulcus, right lateral occipital cortex and left parahippocampal gyrus. The ventral seed, residing in the calcarine sulcus, was connected to the left primary auditory cortex. The executive control seed, residing in the right superior occipital gyrus was uniquely connected to bilateral intraparietal sulci and frontal eye fields, and to the right superior frontal cortex. Finally, the long-term memory seed, residing in the right cuneus, was uniquely connected the right lateral occipital cortex,

right inferior somatosensory cortex and to regions in the right thalamus ($p<0.01$; voxelwise FDR-corrected; Figure 2.2.1 a).

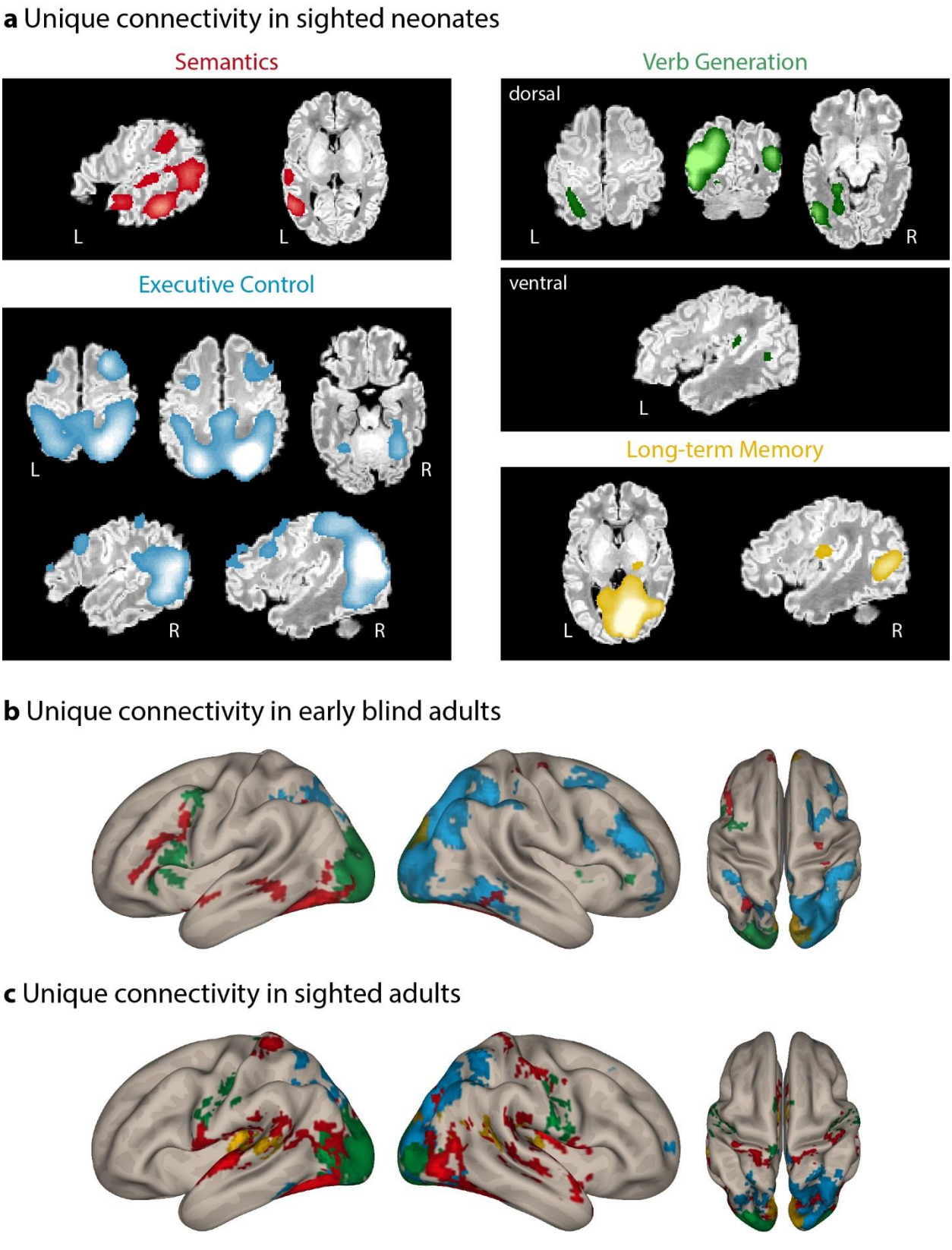


Figure 2.2.1 – Unique functional connectivity in neonates and adults

Significant group-level functional connectivity using semi-partial correlation coefficients. **a** in sighted neonates, several slice views showing maps overlaid on a neonate brain normalized to a template space representing neonates at the gestational age of 40 weeks. Voxelwise threshold was set to p<0.01 FDR-corrected. **b** in early blind adults (adapted from Section 2.1, Figure 4), and **c** in sighted adults (adapted from Section 2.1, Supplementary Figure 3), surface views showing maps on semi-inflated surfaces in MNI space. Voxelwise threshold was set to p<0.005 and all maps are clusterwise corrected (FDR p<0.05).

2.2.3. Discussion

Three main findings emerged from the connectivity results in neonates. First, dorsal seeds (executive control and verb generation) were connected to the bilateral intraparietal sulcus and the parahippocampal gyrus. On top of that, the seed in the right superior occipital gyrus (executive control) was connected to the frontal eye fields and the right fronto-parietal executive network. The resemblance between the fronto-parietal connectivity of the executive control seed in the blind and the neonates is striking. Noticeably, this connectivity pattern in neonates differs from the observed connectivity in the sighted, which is limited to the posterior parietal cortex. This finding supports our hypothesis and is in line with the proposal that visual deprivation may lead to the repurposing of innate connections that would have been otherwise used for the top-down modulation of visual processing (e.g. by attention; Egner and Hirsch 2005) or pruned (e.g. Bourgeois and Rakic 1993). The inferior fronto-occipital fasciculus (IFOF) and superior longitudinal fasciculus (SLF) are candidate tracts that could underlie the observed results (Forkel et al. 2014).

Second, the seed in the left ventral stream (semantics) was connected to the lateral temporal cortex and angular gyrus which are regions involved in language processing in general and are sensitive to semantics in particular (Binder and Desai 2011). When considering the connectivity of the ventral (semantics) seed in the three groups, a complex picture emerges. Neither left inferior frontal connectivity, evident in the blind, nor early auditory and somatosensory connectivity, evident in the sighted, were found in neonates. Connectivity to the superior temporal cortex, however, was evident in the three groups. In normal adults, studies have shown that the left fusiform gyrus is anatomically connected to language regions including the lateral temporal cortex and the angular gyrus (Bouhali et al. 2014). Furthermore, those connections are thought to precede literacy and predict the eventual location of word-selective regions in the fusiform gyrus (Saygin et al. 2016). In fact, those connections are thought to provide the necessary infrastructure for a prospective visual region to become specialized in processing language symbols (Dehaene and Cohen 2007; Hannagan et al. 2015). Finding those connections at birth supports the concept that connectivity biases, along with sensory input, determine cortical specialization. Hence, the combined effect of connections from the fusiform gyrus to language

regions and normal visual input eventually lead to specialization for visual orthography whereas such connections with no visual input would lead to non-visual, language-related, functional specialization. Indeed, some authors speculated that the visual word-form area (VWFA), residing in the posterior fusiform gyrus, could serve as a gateway for linguistic information to enter the visual system (Bedny 2017).

Third, seeds in early visual cortex (verb generation and long-term memory) were uniquely connected to auditory and somatosensory regions besides their occipital connectivity. This is in line with results in a different group of neonates where, using a clustering analysis on functional connectivity, we found that medial occipital regions, including primary and ventral secondary visual cortices are connected to primary auditory and sensory cortices (Bartfled, Abboud et al. under revision; Appendix A). The difference in connectivity between blind adults and sighted neonates might be related to the direct influence of visual input relayed by the thalamus to the early visual cortex. Indeed, thalamic synchrony at birth is thought to drive synchrony in primary sensory cortices that could give rise to the observed functional connectivity in neonates (Alcauter et al. 2014). Conversely, when visual input does not feed the system, a different developmental path would be followed. To our surprise, we found no one-to-one overlap with the connectivity observed in the sighted. However, this could be possible because relationships between functional brain networks (e.g. visual and auditory) evolves over time during the first years of life (reviewed in Gilmore et al. 2018). It is also possible that differences in seed definition between the groups could contribute this variability. Indeed, it has been shown that the strength and extent of auditory-visual functional connections, thought to mediate multisensory processing, depends on the anatomical position tested (Eckert et al. 2008). An investigation focused on the interaction between early sensory regions at birth can help clarify the observed differences.

Last, we also coincidently found connectivity between the lateral occipito-parietal cortex and the parahippocampal gyrus, home to the parahippocampal place area (PPA). The PPA is known to be selective for scenes and large nonmanipulable objects (He et al. 2013; Grill-Spector and Weiner 2014). The observed connectivity at birth is in line with similar functional connectivity patterns between the parahippocampal gyri and the posterior intraparietal sulcus and superior parietal lobe seen in adults and is thought to contribute to the cognitive ability of spatial navigation (Hutchison et al. 2014).

A major limitation of this investigation lies in the lack of formal comparisons between the three subject groups. Nonetheless, it is included in this dissertation as a proof-of-concept with preliminary evidence. Establishing anatomical equivalence between adults and neonates, is not a straightforward process because cortical regions are not fully developed and white-matter connections are not entirely mature.

However, a coarse anatomical parcellation, for example, might lead to roughly comparable regions across groups. Future studies could benefit from such a parcellation for performing formal statistical comparisons across groups. Moreover, robustness to the exact seed definition should be evaluated as connectivity measures can differ substantially between neighboring regions (Cohen et al. 2008). Finally, a possible confounding factor in the comparison of resting-state connectivity between neonates and adults is the fact that MRI data can only be acquired in neonates as they sleep, while our adult cohort was awake during those sequences. As sleep has been demonstrated to influence resting-state networks (Tagliazucchi and Laufs 2014), future studies might wish to investigate any confounds related to the comparison between awake adults and sleeping neonates.

To summarize, our results indicate that connectivity at birth may explain certain adaptive plastic changes seen in adulthood. Such changes seem to result from a conjunction of innate connectivity constraints and the input profile of each neuronal circuit. This will be further elaborated upon in the general discussion **(Chapter 4)**.

2.2.4. Methods

The following is based on the "Data Release Documentation" of the dHCP release v1.1 (https://data.developingconnectome.org/downloads/documentation/DataReleaseDocumentation.pdf).

Subjects

Infants were recruited and imaged at the Evelina Neonatal Imaging Centre, London. Informed parental consent was obtained for imaging and data release, and the study was approved by the UK Health Research Authority. All infants were born and imaged at term age (37-44 weeks of age). The dataset initially contained 40 subjects, out of which three were removed due to technical issues concerning the transformation to standard space. The remaining 37 subjects included 24 males and 13 females for whom gestational age at birth was 39.03±1.68 weeks (mean±std) and gestational age on the scanning day was 39.96±2.12 weeks.

Imaging

Imaging was carried out on 3T Philips Achieva (running modified R3.2.2 software) using a dedicated neonatal imaging system which included a neonatal 32 channel phased array head coil. The infants were imaged in natural sleep. Anatomical images (T1w and T2w), resting state functional (rs-fMRI) and diffusion (dMRI) acquisitions were acquired in a total examination time of 63mins.

T2w and inversion recovery T1w multi-slice fast spin-echo images were each acquired in sagittal and axial slice stacks with in-plane resolution 0.8x0.8mm 2 and 1.6mm slices overlapped by 0.8mm. Other

parameters were – T2w: 12000/156ms TR/TE, SENSE factor 2.11 (axial) and 2.58 (sagittal); T1w: 4795/1740/8.7ms TR/TI/TE, SENSE factor 2.27 (axial) and 2.66 (sagittal).

High temporal resolution fMRI developed for neonates used multiband (MB) 9x accelerated echo-planar imaging and was collected for 15 minutes, TE/TR=38/392ms gave 2300 volumes, with an acquired resolution of 2.15mm isotropic. No in-plane acceleration or partial Fourier was used. Single-band reference scans were also acquired with bandwidth matched readout, along with additional spin-echo acquisitions with both AP/PA fold-over encoding directions.

Preprocessing

Anatomical volumes were bias corrected, brain extracted and segmented. The segmentation included gray matter, white matter and cerebrospinal fluid (CSF) masks. The functional dataset was treated through a preprocessing pipeline that included correction for susceptibility distortions, motion correction, registration, and ICA denoising (Fitzgibbon et al. 2017). Both anatomical and functional volumes were warped to a standard template space representing a neonate at 40 weeks of gestational age (Serag et al. 2012). Detailed information about the previous pre-processing steps can be found online in the “Data Release Documentation” linked above.

Resting-state functional volumes were spatially smoothed (3mm FWHM, isotropic). Then, in similarity to the adults, preprocessed using CONN toolbox (Whitfield-Gabrieli and Nieto-Castanon 2012) in order to bring spurious correlations to a minimum. We applied linear trend removal to correct for signal drift and band-pass filtering (0.008-0.09Hz) to reduce non-neuronal contributions to the spontaneous BOLD fluctuations. Moreover, we used the aCompCor strategy (Behzadi et al. 2007) to define temporal confounding factors extracted from the white matter and CSF.

Data analysis

For each subject, the average time-course of the preprocessed resting-state BOLD signal was extracted from each seed region, and a whole brain correlation map was computed using the semi-partial correlation coefficient. For each seed, those coefficients result from a correlation analysis of its time-course while regressing out the time-courses of all other seeds. Correlation values were then transformed into Z values (Fisher’s r-to-Z). For each seed, the individual Z-maps were entered in a second-level group analysis resulting in a t-map of connectivity (CONN toolbox). Next, maps were corrected for multiple comparisons at the voxel level using false discovery rate (FDR) correction with q=0.01.

2.3. Limitations and perspectives

Functional specialization

In Section 2.1, we studied the activation of blind visual cortex by several cognitive functions. We delineated regions sensitive to different cognitive functions. However, we were not able to formally compare the tasks in order to achieve maps of functional specialization where one task activates more than the others. Several reasons underlie this inability to make formal comparisons. First, partly overlapping cognitive processes. For example, the verb generation contrast included semantic and verbal executive processes. This partly overlaps with the semantics contrast in the speech perception experiment and could potentially use executive resources common to the executive control contrast. Second, different paradigm designs. For example, we used an event-related design in the memory paradigm and a block design in all other tasks. It is not clear whether a comparison between model outcomes resulting from entirely different designs is at all meaningful. Third, it is possible that distinct functions in the visual cortex result in different effect sizes, biasing comparisons towards the functions with the biggest effect size.

Thus, to establish true functional specialization through dissociations, tasks should be designed with emphasis on circumscribed cognitive functions while equating technical considerations such as experiment design and effect sizes.

Individual subjects

In Section 2.1, we were not able to fully explore differences between individual subjects mostly because of the lack of data in each experiment. Motivated to test the biggest number of tasks across subjects, we were not able to prolong each experiment enough in order to reach stable activation patterns in each subject. However, beyond the main effects that we observed, which were the strongest, most common, effects across blind subjects, a certain amount of inter-subject variability could prevail. Therefore, it would be interesting to test a smaller amount of functions for longer time periods in order to have enough data allowing to formally assess if the correspondence between functional dissociations and anatomy is consistent across subjects. This would clarify to what degree is the plastic process consistent across individuals. In addition, it could permit testing whether connectivity measures, at the single-subject level, would be predictive of the novel functional recruitment.

Functional connectivity

In the two studies included in this chapter, we use functional connectivity measures in order to assess connections between regions. Here, it is important to note that functional connectivity is a fancy name that refers to correlations in the spontaneous BOLD fluctuations at rest. Those correlations are thought

to arise due to functional co-activation, reflecting both direct (correlated to anatomical connectivity) and indirect connections (reviewed in Fox and Raichle 2007; and Damoiseaux and Greicius 2009).

The hypothesis we tested on the connectivity-constrained functional reorganization was formulated on the basis of direct anatomical connections. However, we used functional connectivity as a proxy for those anatomical connections, and as a result, our inference might have been also based on indirect connections. Therefore, it would be beneficial to replicate our findings also using structural connectivity, for which the influence on cortical organization would be more straightforward to justify.

Anatomical overlap

Last, one should mention the use of volumetric normalization to MNI space. It has been shown that volumetric alignment of subjects is inferior to surface-based methods that achieve better inter-subject overlap (e.g. Van Essen 2005; Anticevic et al. 2008). The use of surface-based atlases, then, could be more useful in future studies looking at the functional specialization of different anatomical regions across blind subjects.

3. Electrophysiological investigation of language

In this chapter, we focused on language, which is the most studied among the reorganized high-order cognitive functions in blindness. We were motivated by results that show a general sensitivity to semantics (e.g. when comparing words to pseudo-words in our speech comprehension paradigm Section 2.1) to explore two main aspects: 1) whether semantic content is actually coded in the visual cortex of the blind; 2) the time point at which occipital regions intervene during semantic processing.

We addressed those aspects in an MEG experiment where we used a semantic decision task in sighted and blind individuals. This allowed us to probe the spatiotemporal dynamics of semantic access in both groups in order to test the influence of the functional reorganization in the blind on the semantic system.

3.1. Semantic coding in the visual cortex of the early blind

Semantic coding in the visual cortex of the early blind

Sami Abboud[1*], Denis A. Engemann[2*], Laurent Cohen[1, 3]

[1] Institut du Cerveau et de la Moelle épinière, ICM, Inserm U 1127, CNRS UMR 7225, Sorbonne Université, F-75013, Paris, France

[2] Parietal project-team, INRIA, Universite Paris-Saclay, 91120, Saclay, France

[3] Service de Neurologie 1, Hôpital de la Pitié Salpêtrière, AP-HP, F-75013, Paris, France

*equal contributions

Corresponding author:
Sami Abboud
Institut du Cerveau et de la Moelle épinière
47 Boulevard Hôpital, 75013 Paris, France
Phone: +33 (0)1 57 27 42 37
E-mail: s@mi.nalisa.net

Correspondence may also be addressed to Denis A. Engemann, E-mail: denis.engemann@gmail.com

Abstract

Enhanced activation has been observed repeatedly in the occipital cortex of the blind, during a variety of tasks that involve verbal material, including tasks that concern word meaning. Those studies however did not establish whether such activations are related to the presence of actual semantic content. In order to address this question, we investigated the spatiotemporal unfolding of access to word meaning in early blind and sighted individuals, using MEG, during a semantic decision task. We found that brain responses to auditory words evolved in the same time window in the blind and the sighted and that only in the blind, responses extended to occipital regions. Then, using a series of univariate and multivariate analyses we showed that semantic categories could be discriminated in both groups at the single-trial level in the same time window. Crucially, the signal collected in the blind over a cluster of occipital sensors differed across semantic categories in agreement with the unique contribution of the occipital cortex to the multivariate decoding of meaning. This indicates that occipital regions in the blind actually carried semantic information. Finally, using cross-subject decoding, we also found higher variability in the cerebral implementation of semantic categories in the blind than in the sighted. We conclude that visual deprivation during development expands the functional repertoire of the occipital cortex to the representation of word meaning.

3.1.1. Introduction

Blindness from birth abolishes visual input into the occipital cortex and initiates a chain of events that leads to its involvement in various non-visual functions (reviewed in Ricciardi and Pietrini 2011; Voss and Zatorre 2012; Bedny 2017). Language processing, a high-order cognitive function, is among those who recruit the occipital cortex of the early blind. Both general language features such as speech comprehension, word generation and verbal memory, and more subtle features such as sentence-level structure and syntactic complexity were found to activate the occipital cortex (e.g. Amedi et al. 2003; Bedny et al. 2011; Lane et al. 2015).

Along those lines, some findings suggest that the occipital cortex in the blind also plays a role in semantic processing. First, visual regions as early as primary visual cortex (V1) are activated when contrasting heard words and pseudowords (Bedny et al. 2011). Second, stimulating the occipital pole using repetitive transcranial magnetic stimulation leads to semantic errors during verb generation (Amedi et al. 2004). Third, a contrast between a task involving the semantic content of words and a task of speaker gender identification on reversed words, activates the left fusiform, middle occipital and superior occipital gyri (Noppeney et al. 2003). Finally, the impact of intelligibility of speech, commonly attributed to superior temporal gyrus functions, was found to be associated with the right posterior calcarine sulcus when using a speech tracking paradigm (Van Ackeren et al. 2018).

However, showing occipital activation during a verbal semantic task versus baseline, or finding differential activation to conditions requiring different levels of semantic processing, does not amount to demonstrating the existence of actual coding of word meaning in those regions. In sighted individuals, semantic information is coded across an extensive distributed network of regions that hold domain-specific information. Those include the lateral and ventral temporal cortices, the inferior parietal cortex and the prefrontal cortex but not primary sensory cortices (Huth et al. 2016; Ralph et al. 2017). In the blind, the same organization seems to prevail. Namely, regions which represent meaning in the sighted do so in the blind as well. Thus, the activation profile of the left middle temporal gyrus during similarity judgments on verb pairs from three different semantic categories is similar across blind and sighted (Bedny et al. 2012). Moreover, in a task involving semantic content, when comparing words referring to hand actions (e.g. tapping) to words referring to sound (e.g. siren), vision (e.g. flash) and motion (e.g. gallop), both blind and sighted activated the left posterior middle temporal cortex. When comparing words referring to vision to the other categories, both blind and sighted activated the left inferior temporal gyrus (Noppeney et al. 2003). A similar picture also emerges for the organization of the ventral occipito-temporal cortex according to semantic domains, an organization which persists in blindness

(Mahon et al. 2009; Peelen et al. 2013; Wang et al. 2015; van den Hurk et al. 2017). For example, when comparing animals to manmade objects during a size-judgment task, the lateral preference for animals and medial preference for objects can be seen in both blind and sighted (Mahon et al. 2009).

Should one conclude then, that blind individuals maintain a semantic system that is the same as the sighted despite the large-scale plasticity leading to the involvement of their occipital cortex in language processing?

We addressed this question by probing the spatiotemporal unfolding of semantic access in the early blind. To this end, we acquired magnetoencephalography (MEG) recordings in blind and sighted subjects while they performed a semantic decision task to heard names belonging to 3 semantic categories: animals, plants and manmade objects. Using univariate and multivariate analyses on the sensory array and in source-space, we tested whether and when semantic categories could be discriminated in single subjects. We then compared semantic discrimination between the blind and the sighted to look for group differences in semantic processing. Finally, we tested whether the neural implementation of semantic processing is similar across subject and across groups.

3.1.2. Materials and Methods

Subjects

The study included 12 early blind individuals that were either born blind or have lost their sight during the first six weeks of life (7 males; age: 46±16, mean±SD) and 14 sighted controls (7 males; age: 47±15), out of which 12 were matched in sex, age and education level to the blind group. All subjects were native French speakers. None of the blind subject had any form of light perception (Table 1). All subjects signed an informed consent form, were paid for their participation and were naive about the aims of the study. The study was approved by the local ethical committee.

Table 1 – Causes of blindness.

Subject	Gender	Age	Cause of blindness
B01	M	25	Congenital bilateral glaucoma
B02	M	66	Congenital retinis pegmintosa
B03	F	35	Bilateral retinopathy of prematurity
B04	F	28	Micropthalmia
B05	M	48	Retinal detachment
B06	M	44	Unknown
B07	F	54	Bilateral retinopathy of prematurity
B08	M	68	Congenital bilateral glaucoma
B09	M	68	Congenital bilateral glaucoma
B10	F	22	Micropthalmia
B11	M	51	Unknown
B12	F	43	Micropthalmia

Experimental design and Stimuli

Subjects performed an auditory semantic decision task while Magnetoencephalography (MEG) was concomitantly recorded. Stimuli consisted of words from three semantic categories: Animals, Manmade objects and Plants (see Supplementary Table 1 for a full list). The task was divided into blocks during which subjects categorized words belonging to category pairs that were equally distributed across blocks. Each block started with two repetitions of an instruction-to-cue mapping response buttons to the two categories (e.g., “Animal, Left. Plant, Right”). Then, a period of silence (3 s) preceded a list of 60 words with a uniformly jittered inter-stimulus interval (ISI) of 1.3-1.55 s (Figure 1).

Subjects were instructed to respond after each word using their left and right index fingers indicating the semantic category each word belonged to, as fast as they could without sacrificing accuracy. Once the ISI had passed, the next word was presented regardless of the subject response. Each block was followed by 5 seconds of rest. A total of 36 blocks was divided across 12 runs of approximately 7 minutes. Subjects were offered a break every three runs but were granted more or less pauses depending on their reported state of fatigue. The response-mapping was equalized across semantic categories.

The stimuli totaled to 90 unique words (Lexique database; New et al. 2004), 30 per semantic category (Supplementary Table 1). Words were also equalized across three phonemic categories as per their first vocalic phoneme. Those phonemes were the French [a], [e] and [o]. Each semantic category, then, contained ten words with each phonemic category. The list of stimuli was constructed to balance the number of phonemes per word across the semantic and phonemic categories. Put differently, the phoneme count was equally distributed between the nine subcategories, e.g., Animal-[o] (Semantic: $F(2, 81)<1e-30$, $P=1$, ANOVA; Phonemic: $F(2, 81)<1e-30$, $P=1$, ANOVA). In addition, words were matched for frequency of occurrence ($F(2, 81)=0.13$, $P=0.87$, ANOVA; $F(2, 81)=0.9$, $P=0.41$, ANOVA) and number of syllables ($F(2, 81)=0.35$, $P=0.70$, ANOVA; $F(2, 81)=2.17$, $P=0.12$, ANOVA) across both the semantic and phonetic categories. Stimuli and instructions were synthetically generated using the Text-to-Speech function built in OSX 10.9.5 (Apple Inc., CA, United States). Sound files were normalized (maximum amplitude set to -1.0dB) using Audacity (version 2.1.2, http://audacity.sourceforge.net/). Sound file duration did not differ across the three semantic categories ($F(2, 87)=1.04$, $P=0.358$, ANOVA; Tukey's test for the three pairs: $P=0.340$, $P=0.600$, $P=0.897$).

The behavioral responses were analyzed with regard to accuracy and median latencies. Individual success rates were analyzed using a mixed-effects ANOVA with category as within-subject factor, group as between-subject factor and subjects as random factor. Trials with responses faster than 200 ms and slower and 1400 ms and trials with incorrect responses were discarded from the MEG analysis.

Procedure

Subjects first received a short description of the task followed by a practice block outside the magnetically shielded room. Then, the 90 stimuli were played to them in order to ensure they were familiar with all the words. For each subject, unfamiliar words were excluded from the analyses (mean: 1.7± std: 2.2, min: 0, max: 7, words were removed across all subjects). All subjects were blindfolded and kept their eyes closed during the acquisition (except for two blind subjects that were not able to voluntarily control their eyelids). Most subjects underwent a high-resolution anatomical image (T1)

acquisition right after the MEG session. The anatomical volume of the remaining subjects was re-used from a previous study (Abboud et al., under revision; Section 2.1).

Stimulation

We used Psychophysics Toolbox Version 3 (Brainard 1997; Kleiner et al. 2007) for MATLAB (Release 2015b; The MathWorks, Inc., Massachusetts, United States) to implement the experimental procedure. Auditory stimulation was delivered using Nicolet TIP-300 (Madison, WI, USA) with Echodia ER3-14A foam ear tips (France). Button presses were recorded using a Cedrus Lumina LSC-400B controller.

MEG acquisition

MEG signals were acquired using a whole-head MEG system with 102 magnetometers and 204 planar gradiometers (Elekta Neuromag TRIUX MEG system) at a sample rate of 1 KHz and online low-pass filtered at 330 Hz. Electrooculography (EOG) and electrocardiogram (ECG) were simultaneously recorded. ECG electrodes were located at the right clavicle and the lower left quadrant of the abdomen. Vertical EOG electrodes were located above and under the right eye and horizontal EOG electrodes were 2 cm lateral to each eye. The ground electrode was located at the left scapula.

MEG data processing

To clean the MEG data from environmental artifacts temporal Signal Space Separation (tSSS; Taulu et al. 2005) was performed using the MaxFilter tool (Elekta Neuromag). All remaining data processing steps were performed using the MNE software (Gramfort et al. 2013, 2014). Magnetometer and gradiometer data was then band-pass filtered 0.1-15Hz with default filter parameter settings. Eye movement and cardiac artifacts were corrected using Independent Components Analysis (ICA). ICA was estimated on raw data across all runs using the FastICA algorithm (Hyvärinen and Oja 2000). Ocular components were detected using Pearson correlations and cardiac components using cross trial phase statistics (CTPS; Dammers et al. 2008), both, with the MNE-Python default settings.

Anatomical surface reconstruction

Cortical reconstruction and volumetric segmentation of individual T1 weighted anatomical MRI were performed using FreeSurfer (http://surfer.nmr.mgh.harvard.edu/). The following steps were performed: motion correction, average of multiple volumetric T1-weighted images, removal of non-brain tissue, automated Talairach transformation, intensity normalization, tessellation of the gray-matter / white-matter boundary, automated topology correction, and surface deformation following intensity gradients. Based on these individual cortical models we applied deformable procedures including

surface inflation and registration to a spherical atlas which are essential to MEG group level analysis in the source space.

MEG source localization

To estimate cortical neuronal dynamics from the observed sensor array time series we approximated a numeric solution to the biomagnetic inverse problem using cortically constrained Minimum Norm Estimates (MNE) with l2 regularization. The MNE solver yields a linear spatial filter that projects MEG data onto a predefined grid of cortical source locations. Concretely, we computed the MNE solution by fitting the regularized linear regression model to the MEG data based on the forward solution, which quantifies profiles of magnetic field propagations from source locations to MEG sensors from the individual anatomy and conductivity models. As MEG sources primarily reflect population synchrony of big pyramidal layer 4 neurons (Hämäläinen et al. 1993) we placed all source locations on the cortical sheet, hence the cortical constraint prior. We used a single-layer boundary element model (Hamalainen and Sarvas 1989) constrained by the individual anatomical MRI and extracted the cortical surfaces with FreeSurfer with subsampling to about 4098 vertices per hemisphere yielding a surface area of about $24mm^2$ for each source. To minimize violations of the model assumptions of multivariate Gaussian noise, spatial whitening is commonly applied to the MEG data and the forward model based on the noise covariance matrix (Engemann and Gramfort 2015). We estimated the noise covariance from 200ms of baseline segments prior to the stimulus onset using an optimized shrinkage estimator (Engemann and Gramfort 2015). To obtain the final spatial filter we applied depth-weighting (gamma = 0.8) and the loose orientation constraint (loose = 0.2; Lin et al. 2006), both default settings in MNE-Python. This constraint was a compromise between pooling the current orientations and relying on the correctness of the individual curvature information when computing the sign of the signal by weighting the source variances of three dipole components that define the tangent space of the cortical surfaces. We then set the regularization parameter controlling the *lambda2* following the MNE software's standard practice of dividing 1 by the squared signal-to-noise ratio ($1/SNR^2$), where the SNR of event-related data is conventionally assumed to be 3. To make solutions more comparable across subjects, we applied dynamical statistical parametric mapping (dSPM) noise normalization (Dale et al. 2000) which recasts the estimated source current amplitudes relative to its noise-floor, yielding a pseudo F-statistic. We, moreover, used the FreeSurfer routines described above to warp the dipole grids from each individual to the FreeSurfer average brain.

As the MNE solutions is linear and consists in a single matrix multiplication it can be applied to either the time-series, complex-valued Fourier coefficients or other linear transforms under conditions of identical

noise. Here we made use of this property to estimate the sources associated with our linear decoding patterns.

To alleviate the multiple comparison problem, prior to performing group-level statistics, we summarized our inverse solution using the Human Connectome Project (HCP) cortical parcelation (Glasser et al. 2016) with 360 functionally-defined regions of interest (ROI) covering the entire cortical surface. Concretely, we averaged the dSPM values for each subject in each ROI.

Machine Learning

We used a multivariate pattern classification approach for decoding semantic category. Accordingly, we trained a linear pattern classifier to approximate a function that maps MEG signals to condition pairs. To estimate out-of-sample performance we employed a seven-fold group cross-validation where grouping ensured that words used during training were never used during testing, hence, enabling category-level inference. We used an l2-regularized linear model with sigmoid loss function (Logistic Regression) with a constant regularization parameter of C = 1 and trained it on all magnetometer and gradiometer sensors without feature selection. Trials were dropped when necessary for equating the number of right and left presses across categories to prevent bias. We considered single sensor topographies time-point by time-point (e.g. King et al. 2014) and assessed performance using the area under the curve (AUC) of the Receiver-Operator-Characteristic by comparing the class probability predicted by the model to the actual condition label. To compute generalization across time, beyond training the classifier using sensor topographies from one time-point, we also classified at all other time-points from each classifier. Finally, for cross-subject generalization, we used leave one subject out cross-validation, whereas, for cross-group generalization we trained the classifier on group A and tested on group B and vice-versa. Binary decoding was performed on the three category pairs whose results were then averaged. All machine learning was performed using the scikit-learn software (Pedregosa et al. 2011).

To facilitate interpretation of the learned model parameters, which, due to their conditional nature, may reflect either noise or signal, we marginalized the parameters by multiplication with the feature covariance (Haufe et al. 2014). This resulted in the classification patterns for each category pair. We then estimated the sources underlying the patterns by applying the linear MNE inverse operator. To satisfy the empirically estimated noise model obtained from covariance estimation and preserve correct scaling of the inverse solution, we summed the pattern and the evoked response prior to source localization. We then reconstructed the pattern of each category pair by subtracting the corresponding source localized evoked response. We then considered absolute values, as the sign of this contrast should be driven by individual source geometry, which would not add up across subjects. As a result, we

obtained a cortical map indicating the strength of the contributions to either negative or positive model coefficients. Finally, in order to assess the lateralization of the classification patterns in source space, for each subject, we first subtracted the right hemisphere from the left hemisphere and vice versa. Then, for each ROI in source-space, we computed the percentage of the subjects from each group where the value of the difference was above 0.5.

Statistical Inference

Sensor Space

We assessed category discrimination within subjects and between groups using non-parametric permutation clustering tests (Maris and Oostenveld 2007). Within subjects, we used the F-test for independent samples as contrast function in the non-parametric test. We then contrasted the ensuing sensor-wise F-statistics at the group level using the t-test for independent samples with the permutation-clustering test. Settings were consistent with the values suggested in documentation of the MNE software (Gramfort et al. 2014).

Source space

To obtain ROI-wise inference, we then contrasted groups using t-tests for independent samples and obtained inference by comparing the observed t-value against an empirical distribution of t-values under the H0 obtained from 10000 label-wise permutations of the subjects between groups (Groppe et al. 2011). Multiple comparisons we adjusted using FDR-control (Benjamini and Hochberg 1995; Groppe et al. 2011).

Decoding

To assess the consistency of decoding success we contrasted our pattern classifier against dummy models that predicted independently from the MEG data solely based on the stratification of class-labels. We computed confidence intervals of continuous decoding performance across subjects using the non-parametric percentile bootstrap (Efron and Tibshirani 1994) over 4000 bootstrap replica obtained from drawing n samples with uniform probability. To obtain dependable p-values, we additionally compared the difference between decoding performance and a dummy classifier and the decoding performance between groups using paired t-tests against an empirically estimated distribution under the null hypothesis using 10000 permutations.

3.1.3. Results

Behavior

Performance in the semantic decision task was high in both groups (Blind: 91.0±6.6%, Sighted: 94.4±4.7%). The main effects of group and category, and the group × category interaction were not significant (Group: F(1,24)=2.57, p=0.12; Category: F(2,24)=2.63, p=0.08; Group × Category F(2,24)=2.08, p=0.14; ANOVA). Average response times stood at 0.875±0.077 s in the Blind and 0.806±0.108 s in the Sighted. We found a significant main-effect of category (F(2,24)=26.58, p<1.0e-5), but neither a main-effect of group nor a group × category interaction (Group: F(2,24)=3.45, p=0.08, Group × Category F(2,24)=2.67, p=0.09; ANOVA). A post-hoc Tukey's test showed that the category effect reflects systematically shorter reaction times for plants compared to animals and objects (Animals – Objects: t.ratio(48)=0.728, p=0.748; Animals – Plants: t.ratio(48)=6.646, p<1.0e-4; Objects – Plants: t.ratio(48)=5.918, p<1.0e-4).

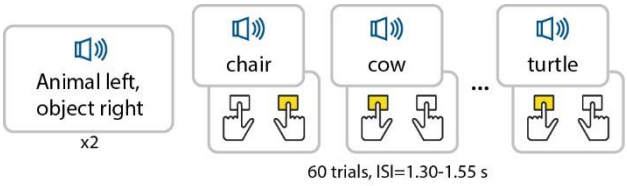


Figure 1 – Semantic decision task. Subjects were first presented with two repetitions of an instruction indicating the mapping between category and response buttons (e.g. Animal, left – Object, right). Then, subjects had to categorize the 60 words to follow according to the mapping. Button mapping was balanced across category pairs and the later were balanced across blocks. Inter stimulus interval was jittered between 1.30 and 1.55 s.

Neural correlates of the semantic decision task

We were first interested in the global differences between the blind and sighted when performing the semantic decision task (Figure 1). Therefore, separately for each group, we pooled together trials from all categories and computed the average evoked-response (Figure 2a-b). We then estimated the cortical sources of this average evoked-response in each subject and averaged their values inside each ROI of the HCP cortical parcellation (Glasser et al. 2016). We found a significant enhancement of activation in the visual cortex during the semantic task when comparing the blind to the sighted. This effect can already be seen in several visual areas early after word onset. However, starting 160 ms, the lateral, medial and inferior sides of bilateral occipital cortex all showed a significant difference between the groups, peaking at 600 ms (P<0.05, FDR-corrected, t-test with non-parametric permutations; Figure 2c). No ROIs showed a significant effect that is stronger in the sighted than the blind.

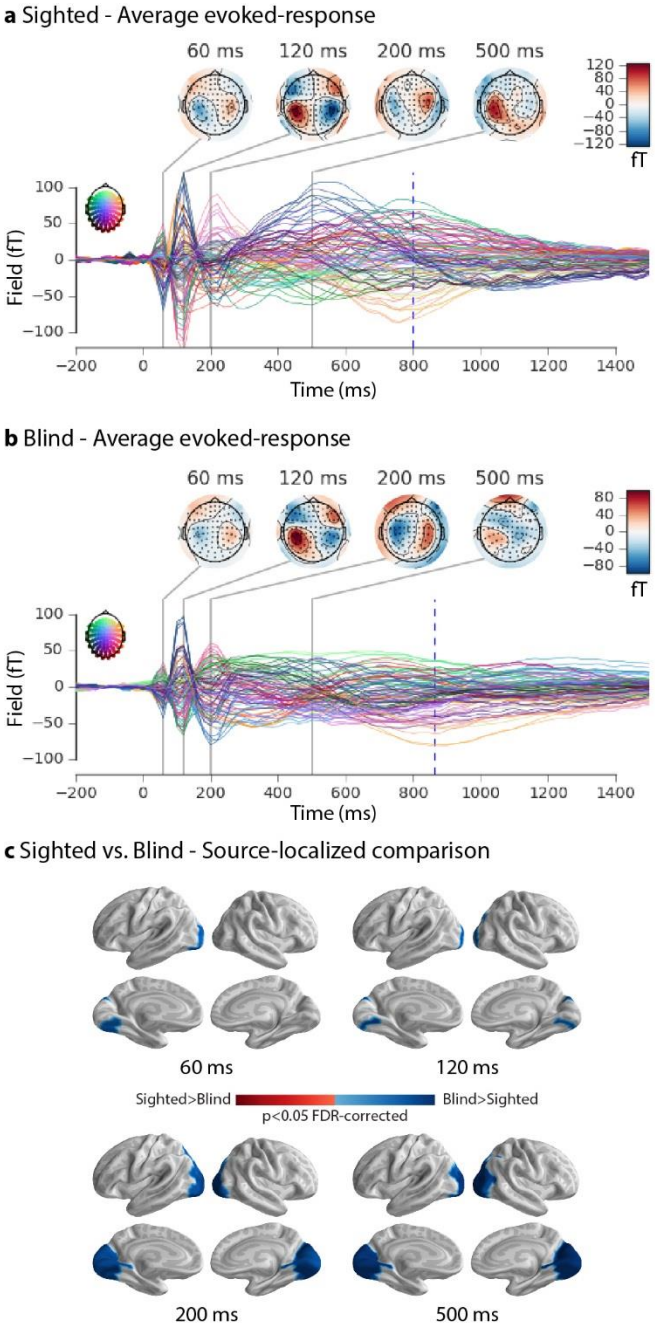


Figure 2 – Neural correlates of semantic processing. a,b | Event-related fields in the sighted and the blind collapsing across stimuli from all categories. X-axis shows time (ms) where zero corresponds to the word onset and Y-axis shows the field strength (fT). **c** | A comparison between the sighted and the blind showing an enhanced activation in the visual cortex of the blind (P<0.05, FDR-corrected, t-test with non-parametric permutations). We did not find evidence for enhanced activity in the sighted compared to the blind. The results suggest that only the blind additionally recruit the visual system during semantic processing.

Neural signatures of semantic category discrimination

An investigation of the effect of semantic category requires optimal temporal alignment of semantic processes across trials and subjects. Therefore, we aligned all successful trials to the response-button press for the analyses to follow. As a first step, we summarized category discrimination using an F-statistic with spatiotemporal clustering on the sensor data in single subjects. We found at least one cluster with significant category discrimination near the button press in all but two sighted subjects (Figure 3a). We then compared individual F-statistics across groups and found one significant cluster where category discrimination was stronger in the blind encompassing posterior sensors between -460 and -20 ms relative to button-press ($P<0.003$, t-test with non-parametric permutation clustering; Figure 3Ba, Bb). To delineate sources showing group differences in semantic category discrimination, we estimated the sources of the three category-pair contrasts (e.g. animals – manmade) for each subject. We then averaged those sources across the three pairs, yielding an individual index of category discrimination, which we compared across groups. Discrimination was stronger in the blind in the lateral, medial and inferior aspects of the occipital cortex continuously between -580 and +380 ms and peaking at -260 ms relative to the button-press ($P<0.05$, FDR-corrected, t-test with non-parametric permutations; Figure 3c). Note that sporadic significant group differences can be seen starting -800 ms.

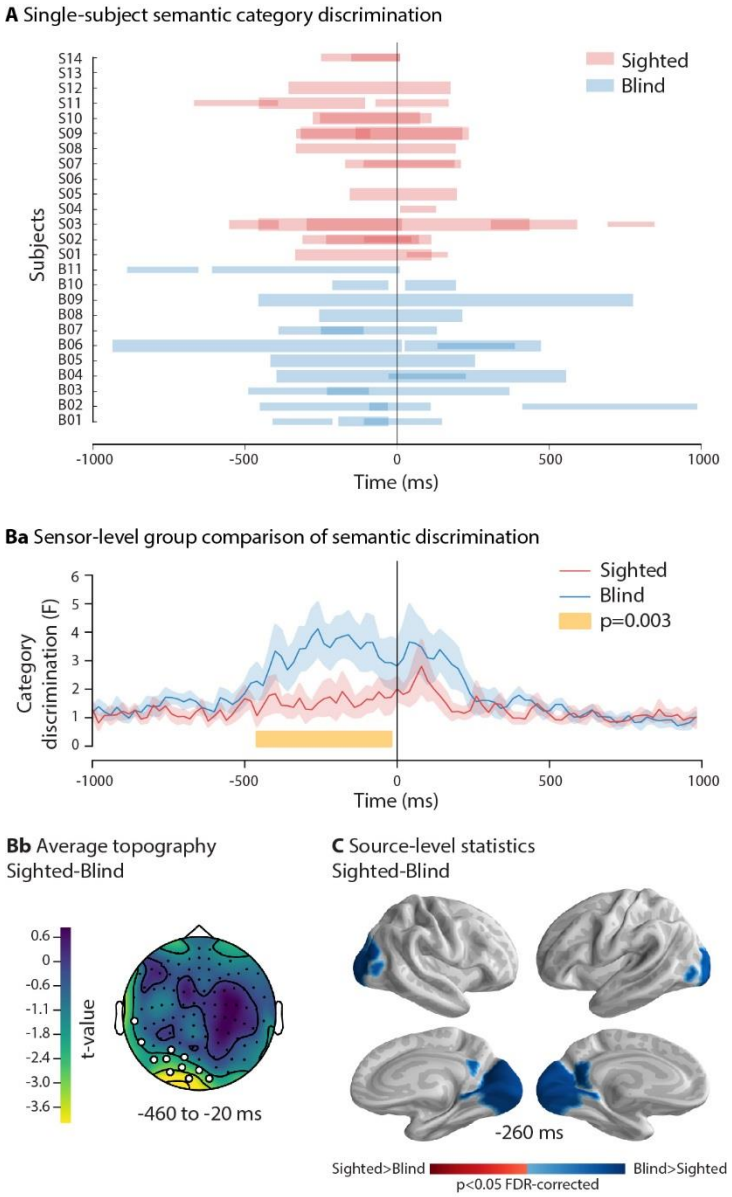


Figure 3 – Neural correlates of semantic category discrimination. A | In single-subjects. X-axis shows time (ms) where zero corresponds to the button press and each row on the Y-axis shows the result of one subject, sighted in red and blind in blue. Each box represents a significant spatiotemporal cluster, box width is inversely proportional to the p-value and cluster overlap renders colors darker. At least one significant cluster near the button press can be seen in all but 2 sighted subjects. **B** | Group comparison. **Ba** | X-axis shows time (ms) where zero corresponds to the button press and Y-axis the average category discrimination in sighted (red) and the blind (blue). The yellow bar indicates the temporal extent of the spatiotemporal cluster with significant difference across the groups (P=0.003, spatiotemporal permutation clustering). **Bb** | The average topography of the group difference in semantic discrimination during the time of the significant cluster (from -460 to -20 ms). Sensors appearing in the cluster are highlighted in white. **C** | The peak difference between the sighted and the blind when comparing the average of all pair-wise contrasts (P<0.05, FDR-corrected, t-test with non-parametric permutations). It shows a stronger effect in the visual cortex of the blind and no regions with a significant effect in the sighted. The results suggest that occipital

sensors were most sensitive to category discrimination in the blind as compared to the sighted and point at specific contributions from the visual cortex.

We then moved to single-trial decoding using multivariate pattern analysis (MVPA). This approach circumvents individual variability in the precise spatial layout of semantic responses, allowing us to study generalization of semantic coding across words, time, subjects and eventually groups. A linear classifier was trained to predict the semantic category from the MEG signal by learning individual information accessible on the sensory array. We started with sequential decoding, training and evaluating one classifier every 20 ms. In the sighted, we observed systematic above-chance single-trial classification in the time-window from -480 to +500 ms relative to the button press (P<0.05, FDR-corrected, t-test against empirical chance with non-parametric permutation testing; Figure 4). In addition, we observed significant single-trial classification, sparsely, at -680, -600, and +580 ms relative to button press. Classification accuracy reached two local maxima: first, before the button press at -80 ms (AUC=0.581, 95%CI=[0.564, 0.596], P=5.0e-4) and second, after button press, at +60 ms (AUC=0.594, CI=[0.560, 0.628], P=5.0e-4). In the blind, we found continuously significant single-trial classification in the time-window from -580 to +540 ms relative to the button press (P<0.05, FDR-corrected; Figure 4). In addition, we also observed above-chance classification sparsely at -800 to -720, -680 to -640, +640, +940, and +940 ms relative to button press. As it was the case in the sighted, also in the blind, we observed two local maxima of classification accuracy: first, before the button press at -160 ms (AUC=0.587, CI=[0.567, 0.603], P<0.0011) and second, after the button press at +80 ms (AUC=0.614, CI=[0.583, 0.645], P<0.0011). Comparing the classification accuracy between the sighted and the blind did not yield significant effects (P=0.178; FDR-corrected). However, a trend to the advantage of the blind was observed at -760 to -720, -640, and -560 to -440 ms (P<0.05 to P<0.005, uncorrected; Figure 4, gray lines). This suggests a virtually equivalent temporal architecture in semantic processing, with weak evidence for earlier processing in the blind.

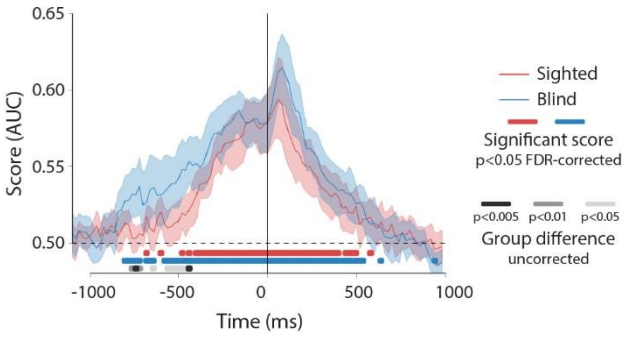


Figure 4 – Single-trial decoding of semantic category discrimination. Classification accuracy scores in the sighted (red) and the blind (blue). Scores reflect the group average of single-subject results across the 3 category pairs. X-axis shows time and (ms) where zero corresponds to the button-press and Y-axis shows the AUC score. Shaded areas indicate bootstrapped 95% confidence intervals. Time-points marked with red (blue) indicate statistically significant prediction scores when compared to empirical chance levels in the sighted (blind; P<0.05, FDR-corrected, t-test with non-parametric permutations). Time-points marked with shades of gray indicate differences between the groups (P<0.05, P<0.01

and P<0.005, uncorrected). The results suggest that the temporal organization of category discrimination was virtually identical in the sighted and the blind.

Due to the significant difference in response time between plants and the other categories, we wished to verify that decoding results did not arise from response time differences. Therefore, we computed the correlation between individual absolute response-time difference in reaction time and decoding score peaks for all category-pairs across subjects. Weak, negative, nonsignificant correlations were retrieved in both groups (Blind: r=-0.15, P=0.366; Sighted: r=-0.18, P=0.283), providing little evidence for a link between decoding success and the reaction time differences.

In order to better describe the temporal evolution of the processes that underlie this classification, we used temporal generalization, i.e., training and evaluating the classifier at different time points (King et al. 2014). In both groups, what seems to be two temporal regions during which cross-classification was possible were found, suggesting sustained activation (King and Dehaene 2014). The first sustained response lasted from about -300 ms until the button press and the second, shorter, sustained response started at the button press and lasted for approximately 100 ms (Supplementary Figure 1).

To infer from where in the brain the semantic classifier retrieved information, we estimated the cortical sources of the classification patterns. Those patterns are derived from the coefficients of the fitted model used by the classifier (time-point by time-point for each subject) and they reflect the relative contribution of brain regions to the classification process. Put simply, they reveal the sources of information that were used by the classifier. During the entire time period when both groups showed continuous significant classification (i.e. from -480 ms to +500 ms) the most contributing sources common to both groups were the anterior and lateral temporal lobes and the left-predominant inferior frontal cortex (Figure 5a). We compared the groups over the entire time window, finding the visual cortex to be significantly more influential in the blind than in the sighted (P<0.05, FDR-corrected; t-test with non-parametric permutations; see Figure 5b for an illustration at the classification peak in the blind). Conversely, the prefrontal cortex was marginally more influential in the sighted than in the blind (P<0.05, uncorrected; Figure 5b). Results at the three other classification peaks (two in the sighted and one in the blind), all show a similar pattern (Supplementary Figures 2 and 3). Taken together, these results converge with the univariate analysis and provide evidence for semantic category coding in the visual cortex of the blind.

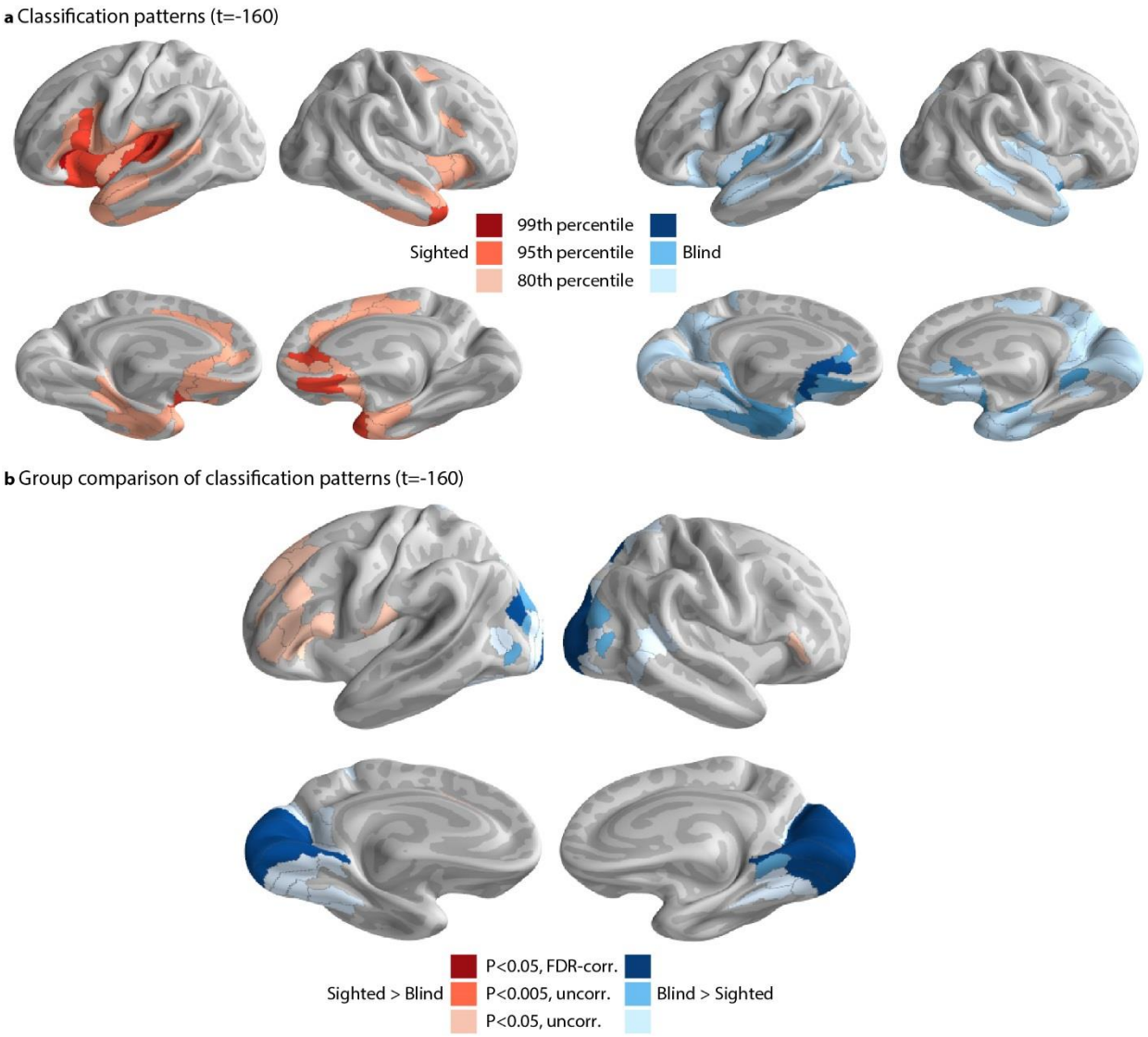


Figure 5 – Cortical sources informative for semantic classification. Cortically reconstructed patterns are shown at the time-point of peak classification accuracy in the blind before button press (-160ms). **a** | The 99th, 95th and 80th percentiles of classification patterns in the sighted (shared of red) and the blind (shades of blue). **b** | A comparison of the classification patterns in the sighted and in the blind. Results show that the bilateral visual cortex is more information in the blind (shades of blue; P<0.05, FDR-corrected, t-test with non-parametric permutations) and the left inferior frontal cortex is more informative in the sighted (shared of red, P<0.05, uncorrected). The results suggest that systematic group-level features informed classification. Cross-subject consistency of neural signatures.

We wished to quantify the degree to which the brain responses underlying correct classification are consistent across subjects. To this end, in each group separately, we repeatedly trained a classifier on all subjects except one that we used to classify. When averaging all predictions, we found above chance cross-subject generalization in the sighted but not in the blind ($p<0.025$ at peak time, t-test with non-parametric permutations; Figure 6). This suggests that sighted subjects process semantic categories in similar ways, while the brain responses of the blind seem to be too variable for cross-subject generalization to succeed. Accordingly, generalization between groups, i.e., training on the all the sighted and classifying using the blind subjects and vice-versa, did not reveal significant generalization.

We tested whether this larger cross subject variability in the blind could stem from the known variability in language lateralization in the blind (Lane et al. 2017). Indeed, we found that in the sighted, there was a consistent left-lateralization in frontal and temporal regions whereas in the blind, lateralization was highly variable, both in the frontal and in the occipital regions (Supplementary Figure 4).

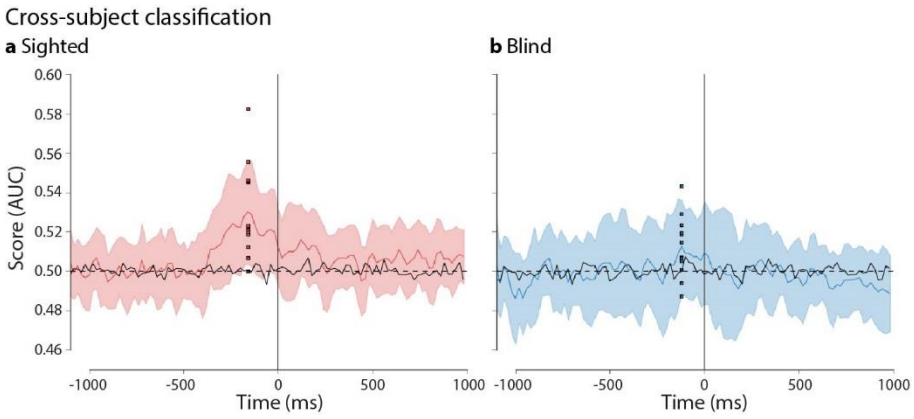


Figure 6 – Cross-subject generalization. a,b | Classification accuracy across subjects in the sighted and the blind. X-axis shows time and (ms) where zero corresponds to the button-press and Y-axis shows the AUC score. The black lines represent decoding accuracy using the dummy models. Shaded areas indicate standard deviation across subjects. In each graph, individual values are plotted at the time-point of peak AUC score reflecting classification success of individual subjects. The results suggest that patterns related to category discrimination were systematically more consistent in the sighted than the blind.

3.1.4. Discussion

Summary

Enhanced activation versus baseline has been observed repeatedly in the occipital cortex of the blind, during a variety of tasks that involve verbal material (see Bedny 2017 for a review), including tasks requiring access to word meaning (e.g. Noppeney et al. 2003). Those studies however did not establish whether such activations are related to the presence of actual semantic content, or to non-specific task-related processes. In order to address this question, we investigated the spatiotemporal unfolding of access to word meaning in early blind and sighted individuals, using MEG, during a semantic decision task. In the blind, brain responses to auditory words evolved in the same time window as those observed in the sighted (Figure 2ab). Univariate analyses showed that responses in individual subjects differed across semantic categories, again in the same time window in both groups (Figure 3a). In the blind only, responses extended to occipital regions (Figure 2c). Crucially, the signal collected in the blind over a cluster of occipital sensors differed across semantic categories, indicating that occipital activations actually carried meaning-related information (Figure 3b). Multivariate analyses confirmed that semantic categories could be discriminated in both groups at the single-trial level in the same time window (Figure 4), and that the occipital cortex of the blind had a unique contribution to the decoding of meaning (Figure 5). Finally, using cross-subject decoding, we also found higher variability in the cerebral implementation of semantic categories in the blind than in the sighted.

The experimental design ensured that category discrimination cannot be attributed to any low-level features: Word frequency, number of phonemes, number of syllables, physical duration, and response hand were carefully equated across categories. Moreover, as spoken words may vary in the precise position of their identification point, we mitigated the corresponding inter-item variability by aligning MEG epochs to the button press. Finally, in a control analysis, we checked that differences in response latency could not explain discrimination performance in individual participants. Hence, it is safe to conclude that we actually decoded semantic information and not a correlated feature.

The spatiotemporal unfolding of semantic access

The temporal unfolding of semantic access is quite similar in the blind and in the sighted. This is visible in univariate analyses showing discrimination of word categories in individual subjects (Figure 3a), as well as in multivariate decoding (Figure 4). In both groups, semantic decoding clearly overlaps with the usual time window of the N400 component, which is thought to reflect access to word meaning in both the auditory and the visual modalities, based on a huge experimental literature (Kutas and Federmeier

2011). The broad temporal extent of the N400 covers stimulus-related activity in the semantic system, with incremental convergence on specific word meaning, modulated by task demands, context and expectations. For instance, in sighted participants, Travis et al. (2013) showed an N400 to auditory words in a semantic matching task, peaking around 400 ms after word onset. Closer to the present task, Chan et al. (2011) were able to cross-decode semantic category between auditory and visual words, mostly in the 400 to 700 ms window. Earlier discrimination of semantic category may be possible in some cases, particularly using intracerebral recording (Chan, Baker, et al. 2011). Interestingly, we observed marginal indications of an earlier onset of effective decoding in the blind than in the sighted. This would be in line with electroencephalography (EEG) evidence that the N400 shows an earlier onset in the blind (Röder et al. 2000). Moving from the temporal to the spatial domain, the sources of semantic decoding which we observed in both blind and sighted (Figure 5a) also match the known sources of the N400 component, i.e., left-predominant temporal and inferior frontal areas (Lau 2009; Chan 2011; Travis 2013). In the blind, there was an additional contribution of the occipital cortex to semantic discrimination, which is compatible with EEG studies showing a less frontal topography of the N400 in the blind than in the sighted (Röder et al. 2000; Glyn et al. 2015). Importantly, this discrimination unfolds in the very same N400 period as in the frontotemporal areas (Figures 3c and 5b), suggesting that occipital activity contributed to actual semantic access and not to some post-decisional cognitive process.

Why did the occipital contribution to word semantics in the blind escape previous studies? As discussed before, some studies have shown general occipital sensitivity to semantic processing without trying to discriminate between semantic categories (Amedi et al. 2004; Bedny et al. 2011). Other fMRI studies, using univariate methods, found differences between word categories in temporal cortex but not in occipital regions (Noppeney et al. 2003; Bedny et al. 2012), or even focused the analyses only on the ventral occipitotemporal cortex (e.g. Mahon et al. 2009). However, two previous studies should be considered as proximate context to the present work. First, Schepers et al. (2012) used MEG to show an effect of semantic congruency in V1 of blind subjects, in the N400 time window, using haptic and auditory presentation of objects. This study showed that semantic processes may indeed be detected in the occipital lobes of the blind with MEG, but did neither use verbal material nor test category discrimination. Second, van den Hurk et al., (2017), also using non-verbal stimuli (audio clips), showed with fMRI that decoding category membership was possible in V1 in the blind. The present study fills the critical gap of demonstrating the contribution of the occipital lobes to word meaning in the blind, in the same time window as conventional semantic processes.

Variability

We found that the occipital cortex of the blind can discriminate semantic categories, but we also found that the signals underlying this discrimination do not generalize across subjects. In contrast, cross-subject generalization was possible in sighted subjects. Blind subjects may differ among them in the contribution of various anatomical regions to semantic coding, but also in the precise small-scale configuration of neural activity within those regions. In support of processing in different regions, we found that classification patterns in the blind showed inconsistent lateralization, whereas in the sighted there was strong left-lateralization in the inferior frontal cortex (Supplementary Figure 4). This is in agreement with previous findings showing that language areas are less left-lateralized in three different groups of blind subjects when compared to sighted subjects (Lane et al. 2017). Therefore, dipolar patterns at different locations across blind subjects resulting from this lack of consistent lateralization could hinder cross-subject generalization. Independently, the configuration of neuronal sources at similar locations across subjects could also differ (e.g. dipoles with the same center but different orientation and polarity), giving rise to distinct dipolar field patterns that would also impair cross-subject generalization. Both scenarios would imply that plasticity could have individual impact in the blind.

Conclusion

Discrimination between different semantic categories showed similar temporal unfolding in blind and sighted individuals. In the blind only, this process involved the occipital cortex in addition to frontotemporal regions. Moreover, it seems that the neural implementation of semantic processing is more variable across blind subjects when compared to the sighted.

Further work is needed to elucidate the exact role of the occipital cortex in semantic processing. Using other tasks, it might be possible to dissociate between a role in the storage of semantic information or in the executive processes manipulating semantic information as suggested by the controlled semantic cognition model (Ralph et al. 2017). Finally, the inter-subject variability we found should be replicated by future studies that could try to understand its sources and implications.

Author Contributions

Conceptualization, S.A., D.E. & L.C.; Methodology, S.A., D.E. & L.C.; Software, S.A., D.E.; Formal Analysis, S.A., D.E; Investigation, S.A.; Writing, S.A., D.E. & L.C.; Visualization, S.A., D.E; Supervision, D.E., L.C.; Project Administration, S.A., D.E & L.C.; Funding Acquisition, D.E., L.C.

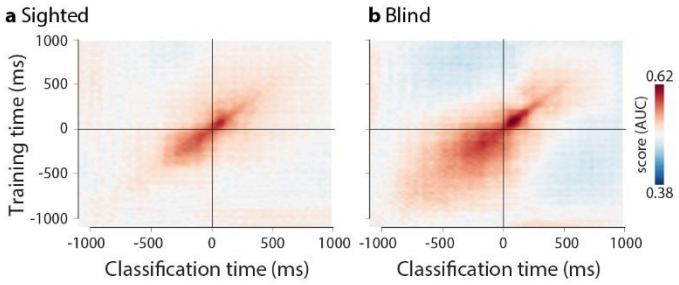
Acknowledgments

The authors would like to thank Celine Cluzeau for coordinating subject recruitment and data acquisition, Alexandre Gramfort, Benjamin De Haas, Guillaume Dumas, Jacobo Sitt, Marijn Van Vliet (in alphabetical order), the Parietal Team and the PICNIC Lab for stimulating discussions and feedback on our work. This study was funded by the “Investissements d’avenir” program (ANR-10-IAIHU-06; to the Brain and Spine Institute), LABEX LIFESENSES (ANR-10-LABX-65; to the vision institute) & “Leshanot Chaim” Foundation (to SA).

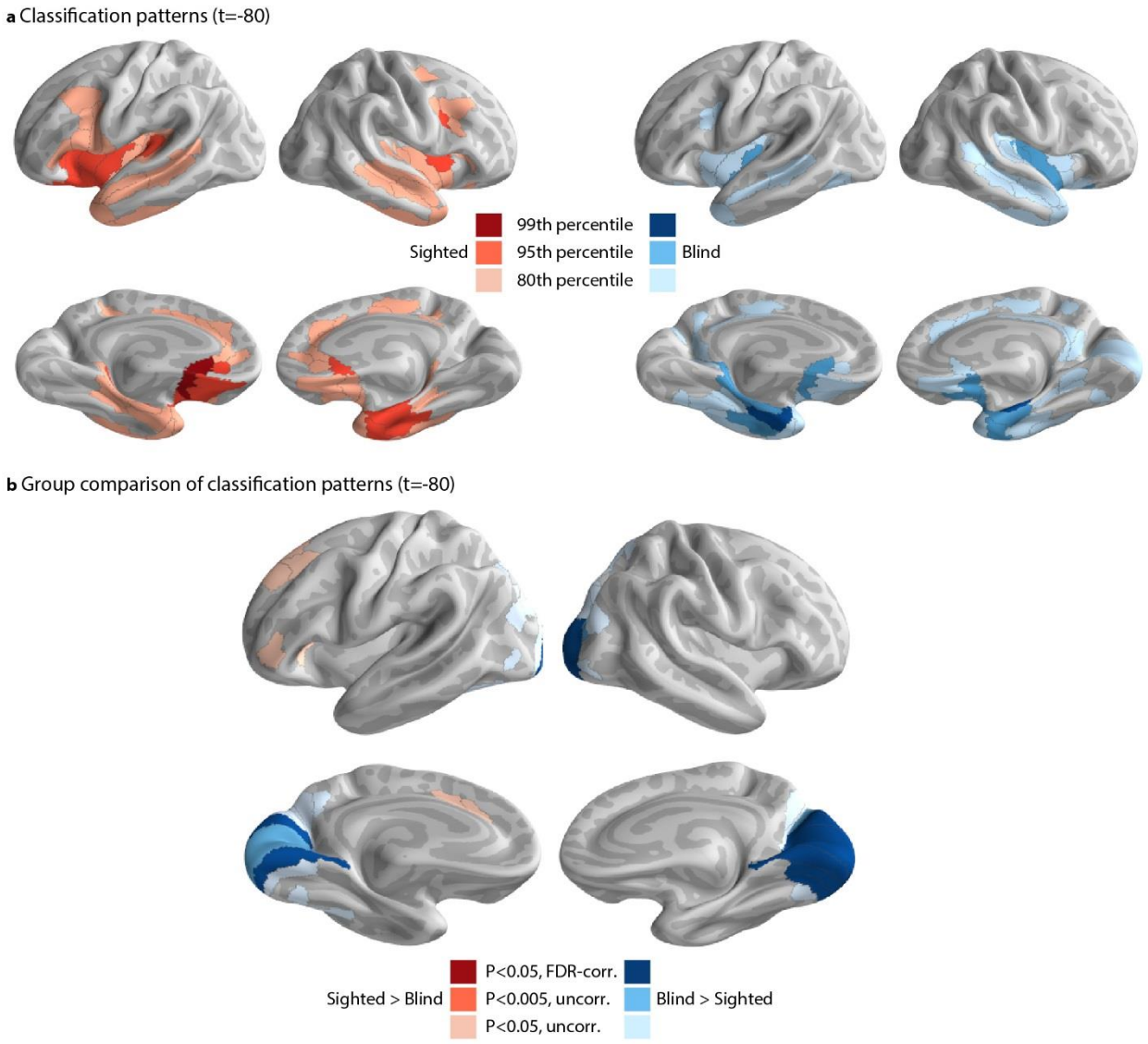
3.1.5. Supplementary information

Supplementary Table 1 – The list of nouns used in the semantic decision task.

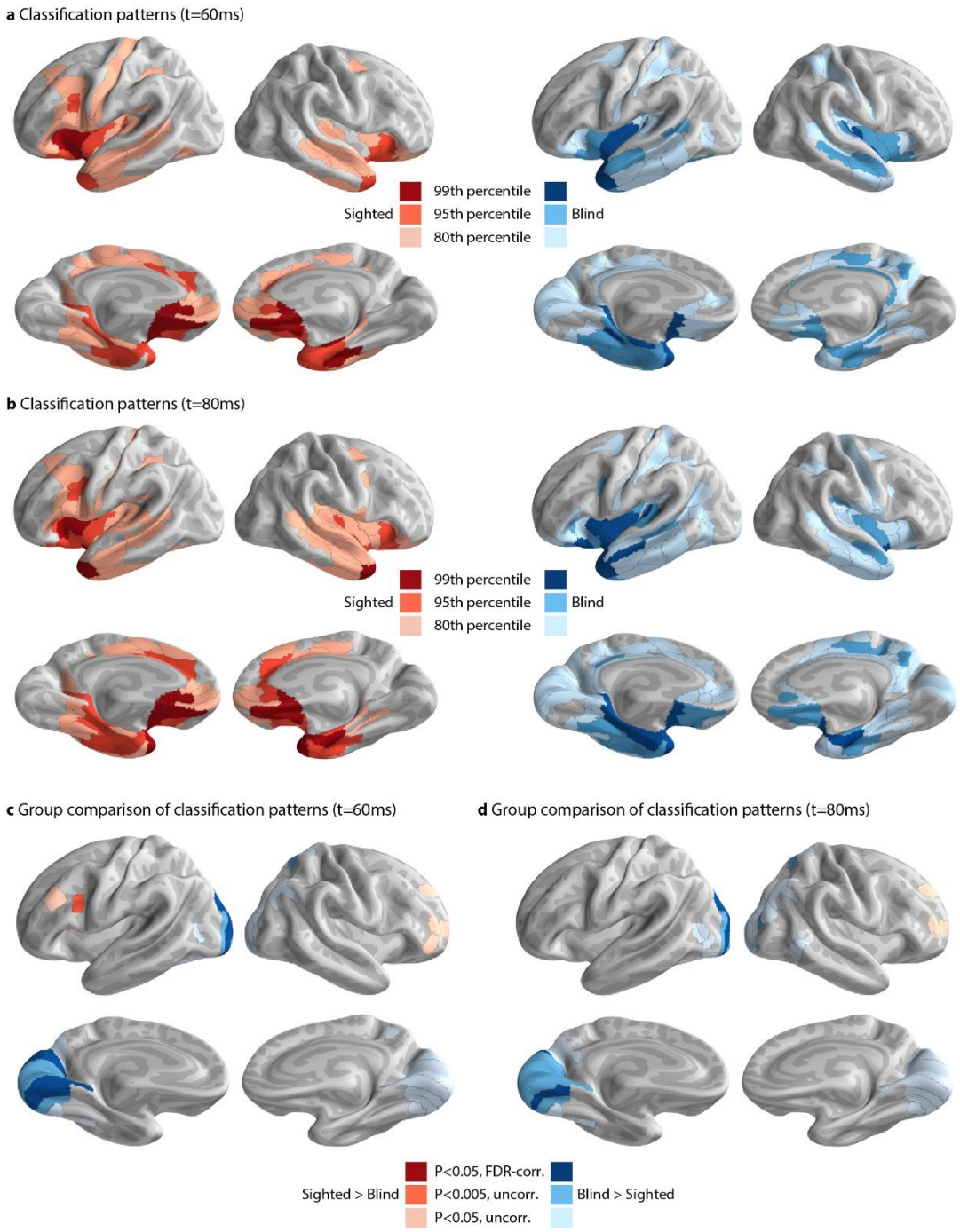
Animals			Manmade			Plants		
abeille	merle	saumon	marmite	fléchette	clochette	mâche	herbe	pomme
baleine	mésange	goéland	manège	épingle	torchon	papaye	cresson	origan
carpe	zèbre	dauphin	armure	écharpe	bobine	carotte	trèfle	laurier
crapaud	bécasse	fauvette	gare	chaise	orgue	lavande	persil	pommier
chameau	chèvre	faucon	barrette	cerceau	chaudron	pastèque	verveine	romarin
sardine	reptile	mollusque	balai	flèche	brosse	sapin	fraise	orange
chamois	blaireau	vautour	cadran	veston	lotion	cannelle	sésame	roquette
chacal	lézard	tortue	chalet	évier	sofa	navet	laitue	olive
hanneton	guépard	brochet	chaloupe	béquille	totem	chardon	mélèze	rosier
vache	aigle	coq	cahier	béton	broche	maïs	raisin	oseille



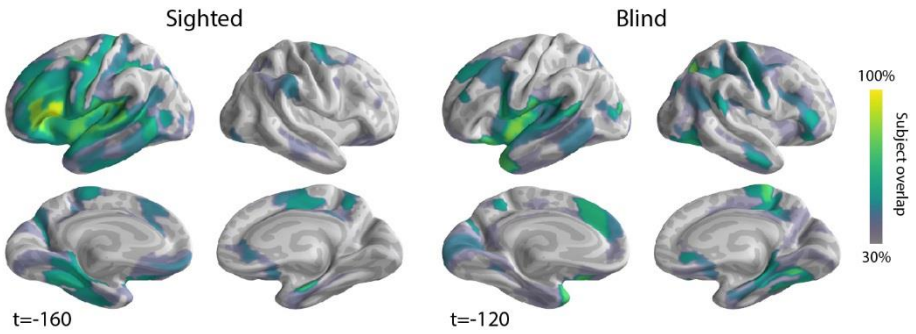
Supplementary Figure 1 – Semantic category time generalization. a,b | For illustrative purposes, we show the results of training the classifier on one time-point and testing on all other-time points in the sighted and the blind . X-axis (Y-axis) shows the classification (training) time and (ms) where zero corresponds to the button-press. The z-axis corresponds to the AUC score.



Supplementary Figure 2 – Cortical sources informative for semantic classification at different time points. Similar to Figure 5. Cortically reconstructed patterns informative for semantic classification at the time-point of peak classification accuracy in the sighted before button press (-80 ms). **a** | The 99th, 95th and 80th percentiles of classification patterns in the sighted (shared of red) and the blind (shades of blue). **b**| A comparison of the classification patterns in the sighted and in the blind. Results show that the bilateral visual cortex is more information in the blind (shades of blue; P<0.05, FDR-corrected, t-test with non-parametric permutations) and the left inferior frontal cortex is more informative in the sighted (shared of red, P<0.05, uncorrected).



Supplementary Figure 3 – Cortical sources informative for semantic classification at different time points. Similar to Figure 5. Cortically reconstructed patterns informative for semantic classification at the time-point of peak classification accuracy in the sighted and the blind after button press (+60, and +80 ms, respectively). **a,b** | The 99th, 95th and 80th percentiles of classification patterns in the sighted (shared of red) and the blind (shades of blue). **c,d** | A comparison of the classification patterns in the sighted and in the blind. Results show that the bilateral visual cortex is more information in the blind (shades of blue; P<0.05, FDR-corrected, t-test with non-parametric permutations) and the left inferior frontal cortex is more informative in the sighted (shared of red, P<0.05, uncorrected).



Supplementary Figure 4 – Inter-subject variability. Inter-subject variability at peak cross-subject classification (-160 ms for the sighted and -120 ms for the blind). Left hemisphere maps show the percentage of subjects with a stronger contribution from the left than the right hemisphere to classification, and conversely for right hemisphere maps. A high overlap in a region reflects its consistent lateralization across subjects. In the sighted, there is a consistent left-lateralization in frontal and temporal regions. In the blind, lateralization is highly variable, both in the frontal and in the occipital regions.

3.1.6. References

Amedi A, Floel A, Knecht S, Zohary E, Cohen LG. 2004. Transcranial magnetic stimulation of the occipital pole interferes with verbal processing in blind subjects. Nat Neurosci. 7:1266–1270.

Amedi A, Raz N, Pianka P, Malach R, Zohary E. 2003. Early “visual” cortex activation correlates with superior verbal memory performance in the blind. Nat Neurosci. 6:758–766.

Bedny M. 2017. Evidence from Blindness for a Cognitively Pluripotent Cortex. Trends Cogn Sci. 21:637–648.

Bedny M, Caramazza A, Pascual-Leone A, Saxe R. 2012. Typical Neural Representations of Action Verbs Develop without Vision. Cereb Cortex. 22:286–293.

Bedny M, Pascual-Leone A, Dodell-Feder D, Fedorenko E, Saxe R. 2011. Language processing in the occipital cortex of congenitally blind adults. Proc Natl Acad Sci. 108:4429–4434.

Benjamini Y, Hochberg Y. 1995. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Stat Soc Ser B Methodol. 289–300.

Brainard DH. 1997. The Psychophysics Toolbox. Spat Vis. 10:433–436.

Chan AM, Baker JM, Eskandar E, Schomer D, Ulbert I, Marinkovic K, Cash SS, Halgren E. 2011. First-Pass Selectivity for Semantic Categories in Human Anteroventral Temporal Lobe. J Neurosci. 31:18119–18129.

Chan AM, Halgren E, Marinkovic K, Cash SS. 2011. Decoding word and category-specific spatiotemporal representations from MEG and EEG. NeuroImage. 54:3028–3039.

Dale A, Liu A, Fischl B, Buckner R. 2000. Dynamic statistical parametric mapping: combining fMRI and MEG for high-resolution imaging of cortical activity. Neuron. 26:55–67.

Dammers J, Schiek M, Boers F, Silex C, Zvyagintsev M, Pietrzyk U, Mathiak K. 2008. Integration of amplitude and phase statistics for complete artifact removal in independent components of neuromagnetic recordings. IEEE Trans Biomed Eng. 55:2353–2362.

Efron B, Tibshirani RJ. 1994. An introduction to the bootstrap. CRC press.

Engemann DA, Gramfort A. 2015. Automated model selection in covariance estimation and spatial whitening of MEG and EEG signals. NeuroImage. 108:328–342.

Glasser MF, Coalson TS, Robinson EC, Hacker CD, Harwell J, Yacoub E, Ugurbil K, Andersson J, Beckmann CF, Jenkinson M, others. 2016. A multi-modal parcellation of human cerebral cortex. Nature. 536:171–178.

Glyn V, Lim VK, Hamm JP, Mathur A, Hughes B. 2015. Behavioural and electrophysiological effects related to semantic violations during braille reading. Neuropsychologia. 77:298–312.

Gramfort A, Luessi M, Larson E, Engemann D, Strohmeier D, Brodbeck C, Parkkonen L, Hämäläinen M. 2014. MNE software for processing MEG and EEG data. Neuroimage. 86:446–460.

Gramfort A, Luessi M, Larson E, Engemann DA, Strohmeier D, Brodbeck C, Goj R, Jas M, Brooks T, Parkkonen L, Hämäläinen M. 2013. MEG and EEG data analysis with MNE-Python. Front Neurosci. 7.

Groppe DM, Urbach TP, Kutas M. 2011. Mass univariate analysis of event-related brain potentials/fields I: A critical tutorial review. Psychophysiology. 48:1711–1725.

Hämäläinen M, Hari R, Ilmoniemi R, Knuutila J, Lounasmaa O. 1993. Magnetoencephalography - Theory, instrumentation, and applications to noninvasive studies of the working human brain. Rev Mod Phys. 65:413–497.

Hamalainen MS, Sarvas J. 1989. Realistic conductivity geometry model of the human head for interpretation of neuromagnetic data. IEEE Trans Biomed Eng. 36:165–171.

Haufe S, Meinecke F, Görgen K, Dähne S, Haynes J-D, Blankertz B, Bie\s smann F. 2014. On the interpretation of weight vectors of linear models in multivariate neuroimaging. Neuroimage. 87:96–110.

Huth AG, de Heer WA, Griffiths TL, Theunissen FE, Gallant JL. 2016. Natural speech reveals the semantic maps that tile human cerebral cortex. Nature. 532:453–458.

Hyvärinen A, Oja E. 2000. Independent component analysis: algorithms and applications. Neural Netw. 13:411–430.

King J-R, Dehaene S. 2014. Characterizing the dynamics of mental representations: the temporal generalization method. Trends Cogn Sci. 18:203–210.

King J-R, Gramfort A, Schurger A, Naccache L, Dehaene S. 2014. Two distinct dynamic modes subtend the detection of unexpected sounds. PloS One. 9:e85791.

Kleiner M, Brainard D, Pelli D, Ingling A, Murray R, Broussard C, others. 2007. What's new in Psychtoolbox-3. Perception. 36:1.

Kutas M, Federmeier KD. 2011. Thirty Years and Counting: Finding Meaning in the N400 Component of the Event-Related Brain Potential (ERP). Annu Rev Psychol. 62:621–647.

Lane C, Kanjlia S, Omaki A, Bedny M. 2015. "Visual" Cortex of Congenitally Blind Adults Responds to Syntactic Movement. J Neurosci Off J Soc Neurosci. 35:12859–12868.

Lane C, Kanjlia S, Richardson H, Fulton A, Omaki A, Bedny M. 2017. Reduced Left Lateralization of Language in Congenitally Blind Individuals. J Cogn Neurosci. 29:65–78.

Lin F-H, Witzel T, Ahlfors SP, Stufflebeam SM, Belliveau JW, Hämäläinen MS. 2006. Assessing and improving the spatial accuracy in MEG source localization by depth-weighted minimum-norm estimates. Neuroimage. 31:160–171.

Mahon BZ, Anzellotti S, Schwarzbach J, Zampini M, Caramazza A. 2009. Category-Specific Organization in the Human Brain Does Not Require Visual Experience. Neuron. 63:397–405.

Maris E, Oostenveld R. 2007. Nonparametric statistical testing of EEG-and MEG-data. J Neurosci Methods. 164:177–190.

New B, Pallier C, Brysbaert M, Ferrand L. 2004. Lexique 2: a new French lexical database. Behav Res Methods Instrum Comput J Psychon Soc Inc. 36:516–524.

Noppeney U, Friston KJ, Price CJ. 2003. Effects of visual deprivation on the organization of the semantic system. Brain J Neurol. 126:1620–1627.

Pedregosa F, Varoquaux G, Gramfort A, Michel V, Thirion B, Grisel O, Blondel M, Prettenhofer P, Weiss R, Dubourg V, Vanderplas J, Passos A, Cournapeau D, Brucher M, Perrot M, Duchesnay E. 2011. Scikit-learn: Machine Learning in Python. J Mach Learn Res. 12:2825–2830.

Peelen MV, Bracci S, Lu X, He C, Caramazza A, Bi Y. 2013. Tool Selectivity in Left Occipitotemporal Cortex Develops without Vision. J Cogn Neurosci. 25:1225–1234.

Ralph MAL, Jefferies E, Patterson K, Rogers TT. 2017. The neural and computational bases of semantic cognition. Nat Rev Neurosci. 18:42–55.

Ricciardi E, Pietrini P. 2011. New light from the dark: what blindness can teach us about brain function. Curr Opin Neurol. 24:357–363.

Röder B, Rösler F, Neville HJ. 2000. Event-related potentials during auditory language processing in congenitally blind and sighted people. Neuropsychologia. 38:1482–1502.

Schepers IM, Hipp JF, Schneider TR, Röder B, Engel AK. 2012. Functionally specific oscillatory activity correlates between visual and auditory cortex in the blind. Brain. 135:922–934.

Taulu S, Simola J, Kajola M. 2005. Applications of the Signal Space Separation Method. IEEE Trans Signal Proc. 53:3359–3372.

Travis KE, Leonard MK, Chan AM, Torres C, Sizemore ML, Qu Z, Eskandar E, Dale AM, Elman JL, Cash SS, Halgren E. 2013. Independence of Early Speech Processing from Word Meaning. Cereb Cortex. 23:2370–2379.

Van Ackeren MJ, Barbero FM, Mattioni S, Bottini R, Collignon O. 2018. Neuronal populations in the occipital cortex of the blind synchronize to the temporal dynamics of speech. eLife. 7.

van den Hurk J, Van Baelen M, Op de Beeck HP. 2017. Development of visual category selectivity in ventral visual cortex does not require visual experience. Proc Natl Acad Sci. 114:E4501–E4510.

Voss P, Zatorre RJ. 2012. Organization and Reorganization of Sensory-Deprived Cortex. Curr Biol. 22:R168–R173.

Wang X, Peelen MV, Han Z, He C, Caramazza A, Bi Y. 2015. How Visual Is the Visual Cortex? Comparing Connectional and Functional Fingerprints between Congenitally Blind and Sighted Individuals. J Neurosci Off J Soc Neurosci. 35:12545–12559.

3.2. Perspectives

We showed that in the blind, the occipital cortex is not only involved in semantic access, it is also able to discriminate between semantic categories. However, our design and collected MEG data allow a multitude of further directions.

Phonemic category discrimination

As described in Section 3.1.2, the material used in the semantic decision task was also crossed on three phonemic categories that were defined according to the first vocalic phoneme of each noun. For example, the word vache (cow), belonged to the [a] phonemic category; the word pomme (apple), belonged to the [o] phonemic category; and the word reptile (reptile) belonged to the [e] phonemic category.

We tested whether we could discriminate phonemic categories the same way we were able to discriminate semantic categories (by aligning the stimuli to the onset of the phoneme, instead of the button press). Then, we planned to compare the brain regions that contributed to phonemic and semantic category discrimination across groups. Our hypotheses were that first, regions contributing to semantics would differ from regions that contribute to phonetics; and second, both regions would differ between the blind and the sighted.

However, phonemic category decoding was not reliable on the single-subject level. Decoding scores were at or close to chance. On the group level, results were above chance in both groups, but still rather low (AUC < 0.54; Figure 3.2.1). Due to those low decoding scores and unreliable single-subject results, we did not proceed with the localization of the classification patterns. In the material we used, phonemes occur naturally in words, which might have made it more difficult to decode. Indeed, a recent study showing phonemic category decoding used more confined syllables such as /ba/ and /ga/ (Bouton et al. 2018). In addition, in their study the authors used single-trial induced responses to decode phonemes while our attempt used the evoked-responses.

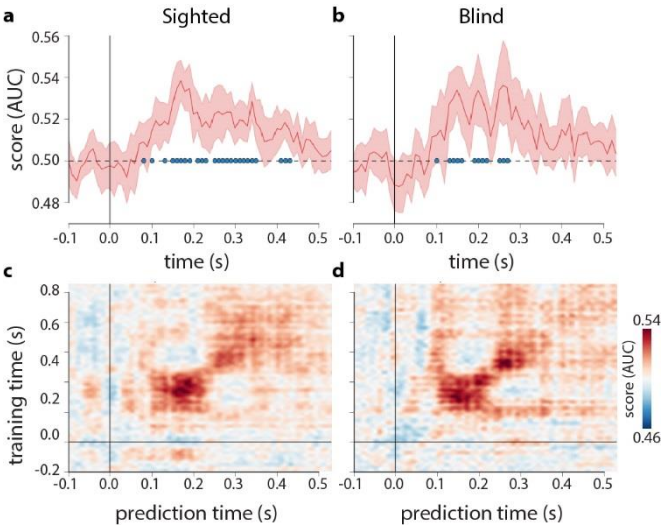


Figure 3.2.1 – Phonemic category decoding. a,b | Classification accuracy scores in the sighted and the blind. Scores reflect the group average of single-subject results across the three category pairs. X-axis shows time and (ms) where zero corresponds to the phoneme onset and Y-axis shows the AUC score. Opaque regions reflect bootstrapped 95% confidence intervals. Time-points marked with blue indicate statistically significant prediction scores when compared to empirical chance levels (P<0.05, FDR-corrected). **c,d** | For illustrative purposes we show the results of training the classifier on one time-point and testing on all other-time points in the sighted and the blind. X-axis (Y-axis) shows the classification (training) time and (ms) where zero corresponds to the button-press. The z-axis corresponds to the AUC score.

Oscillatory activity

So far, we focused on evoked activity either aligned to the onset of the stimulus or the button press. When aligning to such events and averaging across trials, we accentuate evoked activity but average-out asynchronous cortical dynamics. Those dynamics are thought to represent a hierarchical system of brain oscillations that is preserved across mammalian species and supports computation on multiple time-scales within and across brain networks (Buzsáki 2006; Buzsáki et al. 2013). For example, processing in the gamma band points to local computation by the neuronal circuit, while slow bands are interpreted as information exchange between distant regions (Buzsaki and Draguhn 2004).

It has been previously demonstrated that oscillations in the alpha-band are reduced in early blind individuals reflecting their functional reorganization (Kriegseis et al. 2006). Moreover, Schepers et al. (2012) had observed that typical object sounds following a haptic prime generate an induced activity in V1 on the high-gamma band that is influenced by the prime-sound congruency. It would be then interesting to first, test whether we can replicate this finding using heard words and out of a priming paradigm; and second, to test whether this induced activity could be used in order to discriminate semantic categories.

Furthermore, having the time-frequency signal decomposition would allow exploring cross-frequency interactions such as phase-amplitude coupling in addition to cross-region phase-coupling (Siegel et al. 2012). This will permit a better understanding of the reorganized architecture for semantic processing in blindness.

Resting-state

Finally, we also recorded MEG data while subjects were with their eyes closed at rest. Previous studies had found increases of correlations in the delta band (1–3 Hz) and gamma band (76 –128 Hz) oscillations in visual regions, at rest, when compared to the sighted (Hawellek et al. 2013). Using our resting-state data, we wish to extend those results by exploring connectivity measures such as amplitude envelope correlation (Hipp et al. 2012) between the occipital cortex and functionally defined regions in the temporal and prefrontal cortices. This holds the key to a better characterization of brain-scale communication channels in the early blind.

4. General discussion

4.1. Thesis overview

This work was motivated by understanding the fate of the visual cortex when it develops without visual input from birth. Such dramatic conditions during development cause a reorganization in the functional profile of the visual cortex and its brain-wide interactions. We addressed this functional reorganization, both at the level of visual regions and brain-wide functional networks. At the macro-level, we delineated cortical sensitivity to verbal and non-verbal executive functions, speech perception and long-term memory in visual regions using several fMRI experiments. Then, using resting-state fMRI, we provided evidence that unique long-distance connectivity from those regions overlaps with common functional networks in a congruent manner. Namely, visual regions activated by language were connected to the language network while regions sensitive to executive control were connected to the frontoparietal executive network and regions activated by memory were connected to long-distance regions known to be involved in memory (Section 2.1). Then, using resting-state fMRI data in neonates, we provided preliminary evidence for innate connectivity biases that might explain some of the observed functional connectivity in the blind (Section 2.2). Next, we shifted to an investigation of the occipital involvement in semantic processing. Using MEG, we compared the spatiotemporal properties of semantic access between blind and sighted individuals. We demonstrated the ability to discriminate semantic categories in both groups during overlapping time windows. Then, we found that in the blind, also the occipital cortex carried semantic-related information in contrast to the sighted. Finally, using cross-subject decoding, we also found higher variability in the cerebral implementation of semantic categories in the blind than in the sighted (Section 3.1).

In the next sections, I will discuss theories put out to explain the observed phenomena, pointing out the missing pieces in the multi-dimensional puzzle of plasticity in the early blind.

4.2. Computation in the blind visual cortex

Great interest lies in the computation performed by the neural circuits of the reorganized visual cortex in the early blind. Results from animal studies and early findings in humans suggested that plasticity induced by visual deprivation rewires the system in a way that visual cortex receives auditory and tactile input. Auditory tasks such as sound-source localization and tactile tasks such as Braille reading are among the findings seen as support for this suggestion. However, this phenomenon, termed crossmodal plasticity (Rauschecker 1995), by itself, does not explain what computation is actually performed by the different regions of the visual cortex (Bavelier and Neville 2002). Pascual-Leone and Hamilton (2001) attempted to make sense of the observed novel auditory and tactile activations. They argued that the brain of the blind did not just "get its wires crossed" but it is organized in operators computing innate functions. Crucially, those operators are hypothesized to be indifferent to the input modality, thus, they would produce similar output for visual and auditory input alike as long as the task is equivalent. An example of task equivalence is given for spatial discrimination where neurons in sighted visual cortex engaged in localizing visual stimuli, would turn to localize auditory stimuli in a similar fashion when visual cortex is deafferented from retinal input (Pascual-Leone and Hamilton 2001). They also proposed that the cortical structure in the brain is based on a mixture of experts (ME) model where different brain regions (operators), specializing in a certain computation, compete for the ability to perform a set of tasks. This competition is mediated by a gating system, reinforcing regions that prevail in the competition for a specific task and de-weighting other regions. Therefore, leading to the generation of different expert regions, specialized in non-overlapping tasks. For example, hMT+, the motion operator, would be driven by vision in the sighted because vision provides the most reliable input for motion processing. However, in the blind, hMT+ will still be the motion operator but it will receive motion-related information through auditory and tactile inputs whose weights in the gating system will increase. This idea has been recently reiterated also by Bock and Fine (2014). Empirical support for the metamodal organization of the brain is plenty and usually comes in the form of overlapping activations for visual tasks in the sighted and auditory/tactile equivalent tasks in the blind (e.g. Ricciardi et al. 2007; Collignon et al. 2011; Amemiya et al. 2017). For example, spatial localization of visual, auditory and tactile stimuli activate dorsal visual regions such as the middle occipital gyri (Renier et al. 2010; Collignon et al. 2011). This theory, then, predicts that given a visual region, the task that it performs in the blind should be highly similar to what it would perform in the sighted. However, it is not clear at what level

should such metamodal regions represent information in order to be truly indifferent to sensory modality. Intuitively, such a representation cannot be at the lowest-level of sensory signals. Also not clear is how such prediction could be reconciled with findings that implicate the visual cortex in high-order cognitive functions such as language, mathematics and memory (e.g. Amedi et al. 2003; Bedny et al. 2011; Kanjlia et al. 2016). In other words, this theory would predict that common neuronal computations underlie normal V1 functionality in the sighted (e.g. orientation detection), and long-term memory processes observed in the blind. It is possible that such similarity exists at the micro-level of the neuronal circuits, but, to date, there is no published account of a common computation that could give rise to those two different functional activation profiles.

In light of this conflict, authors have concluded that there might be a dissociation where early visual cortex reverts to high-order processing while associative visual cortex keeps a modular organization for processing perceptual functions (Voss and Zatorre 2012). This is in line with a similar concept termed the "reverse hierarchy", alluding to reversal of the common visual processing hierarchy where primary visual cortex processes low-level sensory input that is elaborated in associative visual cortex as it climbs up the visual hierarchy (Amedi et al. 2003; Büchel 2003). However, to the best of my knowledge, there is little evidence supporting a multi-level hierarchy with gradual processing stages in the blind.

In early visual cortex, the plausibility of a completely different computation in the blind is supported by data from animal studies where retinal ablations in utero lead to an unusual cytoarchitectonic organization (Rakic et al. 1991; Dehay et al. 1996). In general, neuronal circuits are thought to emerge through dynamic interactions between genetically determined programs and activity-dependent signals (reviewed in Jabaudon 2017). Therefore, given that activity in V1 is dramatically altered due to the lack of retinal input, it is improbable that neuronal circuits in V1 simply keep their computational properties. This speculation contradicts the proposal that the whole brain, including V1, is organized as operators with innate computations that are resistant to differences in circuit input. The results presented in this thesis, showing that retrieval from long-term episodic memory activates V1 and that semantic category is coded in the occipital lobe, provide support to the speculation that novel computations emerge in the early visual cortex of the blind (Section 2.1, Chapter 3.1).

Our results also challenge the metamodal view outside of primary visual regions. In the speech perception experiment, we found activation in the posterior fusiform gyrus (ventral associative visual cortex), and in the executive control experiment we found activation that peaked in the superior occipital gyrus (dorsal associative visual cortex; Section 2.1). Others have also found high-order activation in the superior and middle occipital gyri to mathematical calculations and linguistic load

(Struiksma et al. 2011; Kanjlia et al. 2016). Those results seem to be contradictory to the spatial metamodal role attributed to those regions. This contradiction calls for a theory that could reconcile both types of findings in blind visual cortex: activation by novel cognitive functions and activation by perceptual functions that seem to be similar to the sighted.

Such a theory has been recently put forward by Bedny (2017) who proposed that the cortex is pluripotent, capable of assuming a heterogeneous range of roles, and its functional destiny is determined by its connections to other regions. Therefore, visual regions with innate connections to frontal and temporal language regions would turn to process language in the blind. Accordingly, regions with strong parietal connections would turn to compute functions such as localization and motion.

The next section is dedicated to the development of functional organization through cortical connectivity constraints.

4.3. Function-connectivity correspondence

The correspondence between function and connectivity lead several authors to propose connectivity-driven cortical organization theories, especially to explain category selectivity in the ventral occipital-temporal cortex (VOTC). For example, Mahon and Caramazza (2011) argued that specialization for semantic domain in VOTC is mediated by its innately determined patterns of connectivity to other brain regions. This view received support from several empirical demonstrations in the sighted where regions selective to different visual categories such as words, faces and places showed distinct white-matter tracts (e.g. Bouhali et al. 2014; Gomez et al. 2015). In addition, structural connectivity has been found to predict cortical selectivity to visual categories (Saygin et al. 2012, 2016; Osher et al. 2016; Wang et al. 2017). According to one suggestion, this category selectivity develops because of differential connectivity patterns to networks computing real-world tasks, which influence the representations needed for items from different categories. For example, orthographic stimuli can appear in different fonts and shapes, necessitating a representation that is invariant for the exact shape while tool representations should encode shape and properties that relate to hand actions (Peelen and Downing 2017). Therefore, it is a conjunction between connectivity and real-word use and not biases to visual features that drives category selectivity in VOTC. An appealing aspect of this theory is that it accounts for the overlapping ventral stream activation in the blind and the sighted for auditory and visual representations of items from the same category, respectively (e.g. Mahon et al. 2009; Peelen et al. 2013; cf. Bi et al. 2016; van den Hurk et al. 2017).

Similarly, Hannagan et al. (2015) proposed the "biased connectivity hypothesis" to address ventral stream specialization for culturally acquired categories such as numerals and words. They argued that learning to read capitalizes on existing connections to perisylvian spoken language areas that are already present early in infancy to generate selectivity for orthography in the visual word-form area (VWFA). Conversely, they argued that selectivity for numbers in the inferior temporal gyrus (number-form area) is a result of innate connections to bilateral intraparietal regions holding non-symbolic numerical quantities (Hannagan et al. 2015). Here again, empirical support can be found in studies showing category selectivity in similar regions of VOTC following equivalent connectivity patterns in both blind and sighted (Striem-Amit et al. 2012; Abboud et al. 2015). Moreover, in the case of the VWFA, there is evidence that the observed connectivity does not result from the functional selectivity but rather precedes it (Saygin et al. 2016).

Those two propositions were motivated by the observed similarities between the VOTC activation profiles in the blind and the sighted. They both proclaim that similar connectivity patterns in blind and sighted lead to similar activation profiles, at least in VOTC. Indeed, no major structural connectivity differences were found between the groups with the exception of the optic radiation, connecting the lateral geniculate nucleus to primary visual cortex (V1), that is atrophic in the blind (reviewed in Bock and Fine 2014). However, as discussed above, differences in the activation profile of the blind visual cortex are not limited to V1, calling for the consideration of additional factors that can influence its reorganization. Indeed, Bendy (2017) hypothesized that in the absence of vision, input from existing innate anatomical connectivity to frontal, parietal and temporal cortices will dominate visual cortex during development. Thus, driving it to adopt novel functions that correspond to its innately connected networks.

Our findings in the blind are in line with this proposal in that they show novel activations by high-order cognitive functions in V1, but also in the fusiform gyrus and in the superior occipital gyrus. More importantly, we also found that the unique functional connectivity from those reorganized regions corresponds to brain networks that support the novel functions (Section 2.1). Those results are in accordance with the suggestion that the novel functions arise from the influence of connectivity biases and the lack of visual input. However, they only reflect the adult-state of the system and therefore cannot rule out that those differences in connectivity are a side effect of the functional reorganization and not the other way round. We addressed this concern by providing preliminary evidence that functional connectivity in neonates can, in some cases, account for the network reorganization in adult blind individuals. We showed unique functional connectivity from the left posterior fusiform gyrus to

prospective language regions in the left hemisphere including the lateral temporal cortex and the angular gyrus and connectivity from the right superior occipital gyrus to the prospective frontoparietal executive network (Section 2.2). This demonstrates that biased innate functional connections already mediate information transfer between the occipital and parietal/temporal/prefrontal cortices at birth. Coupled with the abolition of visual input, those connections could become the dominant input channels to the visual cortex and hence recruit it for their respective computations.

Finally, I would like to conclude this section by speculating that there is a relationship between the importance of visual input for a region and the reorganization it undergoes on the neuronal circuit level. For example, primary visual cortex, most affected from the lack of visual input, would undergo the most dramatic reorganization and therefore acquire novel functions. Conversely, anterior regions in the fusiform gyrus would experience smaller differences in input activity and therefore maintain their usual functions. “The importance of visual input for a region” is a fuzzy concept, which I propose to define by using the portion of input that conveys low-level visual information to the circuit. This could be quantified for neuronal circuits using the portion of their input signal variance explained by the retinal input signal to V1. If future technology would allow the needed measurements, we might be able to test this speculation and eventually estimate the stability of specific neural circuits when facing sensory deprivation.

4.4. General perspectives

This work adds several pieces to the puzzle describing the functional aspects of the blind visual cortex. However, this puzzle is far from completion. In this section, I portray several open questions, discussing their importance and, at times, suggestion experiments to address them.

Function

In this work, we saw that visual regions are connected to cognitive networks in the blind (Section 2.1), however, it is less clear what computation do they actually carry as part of those networks. Assuming that their role is not epiphenomenal, several options are conceivable: 1) they provide additional resources without altering the classical regions; 2) they share the load, creating a balance between the visual and classical regions; 3) they take over whole functionalities. Note that by classical regions I mean the regions that compute that specific function in sighted individuals.

In the domain of language, results show that the activation profile in the dorsolateral prefrontal cortex is preserved in blindness (Bedny et al. 2011; Lane et al. 2015). However, this seems to be different when considering the coding of auditory motion direction. In the blind, auditory direction discrimination accuracy is enhanced in hMT+ and reduced in the planum temporale compared to the sighted (Jiang et

al. 2014). Language results, then, favor option number 1, and most probably rule out option number 3 while motion results could be suggestive of option number 2. In congenitally deaf cats, the selective deactivation of specific cortical structures through cooling provides an elegant way to answer this question (Lomber et al. 1999). In general, congenitally deaf cats show an enhancement in motion detection thresholds and visual localization ability in the periphery when compared to hearing cats. Those advantages in the congenitally deaf cats can be eliminated by cooling their auditory cortex which yields performance levels that are comparable to hearing cuts, providing strong support for option number 1 (Lomber et al. 2010). Those examples demonstrate that the influence of plasticity could vary across functions and species. More work is certainly needed to establish a better understanding of this dynamic.

Moreover, investigating functions that do not migrate to the blind visual cortex is no less important in the endeavor to better understand the plastic process at hand. For example, studies have repeatedly failed to find sensitivity to auditory pitch when compared to sound-source localization in the blind visual cortex whereas such sensitivity was found in the temporal cortex in similarity to the sighted (Renier et al. 2010; Collignon et al. 2011). What could be different about pitch compared to location that would inform us about altered functions in blindness? Some authors had speculated that the more modality-specific the function is, the less potential it has to undergo plastic reorganization following sensory deprivation (Lomber et al. 2010). Accordingly, empirical evidence from congenitally deaf humans shows that color processing, a vision-specific feature, is similar to hearing individuals (Armstrong et al. 2002). This is in agreement with the connectivity driven hypothesis of brain reorganization because functions involving more than one sense should require intra-sensory connections that could be exploited under sensory deprivation. Sensory-specific functions, on the other hand, may lack this connectivity, 'protecting' them from the effects of sensory deprivation. Future studies testing sensory-specific functions could further clarify if such a dissociation exists and whether it is strictly related to connectivity considerations.

Notwithstanding, a similar question could be asked about cognitive functions. What determines the susceptibility of a specific cognitive function to be reorganized in blindness? Beyond connectivity, could this process be influenced by the level of interaction between those functions and vision in sighted subjects? For example, Van Ackeren et al. (2018) made the case for an intensive interaction between language processing regions and visual cortex to enable lip reading, which provides another channel through which language could potentially colonize the visual cortex when deprived from vision. However, studies using working-memory paradigms failed to find visual activation in the blind despite

obvious interactions between frontoparietal and occipital regions supporting visual working-memory in the sighted (Burton et al. 2010; Deen et al. 2015b). In contrast, our study found activation for both verbal and non-verbal executive functions in the blind (Section 2.1), signaling the need for a deeper exploration of the different executive functions and their (non)recruitment of the visual cortex.

Variability

In our MEG study, we showed that semantic processing was more similar across sighted than blind individuals, which showed no cross-subject generalization (Section 3.1). As discussed in Section 3.1.4, this variability could be either at the level of the circuit, where the macro-level organization is similar but the meso/micro-level implementation differs across subjects, or at the level of the network, where regions differ in the exact task performed. It is possible, then, for the latter case that plasticity results in a different balance between occipital and classical regions across individuals that is similar to the balance between hMT+ and the planum temporale described earlier. Taking language paradigms as an example, some individuals would show a stronger use of the occipital cortex when compared to the prefrontal cortex while others would show the opposite effect. When averaged, such a group could still show the effect of interest in both regions, which is compatible with empirical observations showing a similar activation profile in both classical and novel regions (e.g. Bedny et al. 2011; Lane et al. 2015).

We attempted to test this empirically using both our fMRI and MEG data to no avail. Neither using the verb generation nor the speech perception paradigms we were able to find a relationship between the activation levels in visual and dorsolateral prefrontal regions. The same goes for the MEG experiment where we were not able to find a relationship between the individual reliance on visual and prefrontal regions during multivariate category classification. However, this does not rule out the existence of such effects that might need a larger sample in order to duly explore.

One source of variability that is typical to studies in the early blind is the inclusion of subjects with different etiologies, age of sight loss and sensitivity to light perception. However, each combination of these factors could potentially introduce confounding effects to the results. Nonetheless, the limited availability of homogenous cohorts of early blind individuals obliges studies to include subjects with heterogeneous conditions. Despite being a good indicator on the public-health level, this potentially injects sources of inter-subject variability that are not possible to account for. In similarity to most previous studies, we were not able to limit our cohort to one cause of blindness. We did recruit, however, only individuals with very early onset (< 6 weeks) and no light perception. In the future, it would be very useful to systematically compare the organization of V1 across anophthalmic individuals, early blind individuals with no light perception and individuals with sensitivity to light without form

perception (often termed ‘faint light perception’). Understanding differences between those groups, if any, would better inform the conception of future studies.

Longitudinal studies and brain damage

This last point groups two different types of studies because they both suffer from the small number of early blind individuals in the world. Again, this is a good indicator on the level of public health, but both study types could potentially be great sources of insight on the blind brain.

Longitudinal studies in the normal developing brain has brought and still bring insight on brain organization during the first months and years of life (reviewed in Gilmore et al. 2018). The preliminary functional connectivity results in neonates we presented (Section 2.2) show only one snapshot of the organization during the first week of life. However, longitudinal tracking of blind neonates could locate the time points when networks in sighted and blind infants start diverging, revealing interim steps that the system goes through before adult connections and functional specializations are consolidated.

Brain damage, on the other hand, and the neuropsychological insights it brought as a result, were invaluable for the advancement of cognitive science. In the blind, to the best of my knowledge, a single case of alexia for Braille is reported, causally linking VOTC to reading also in the blind (Hamilton et al. 2000). Future incidents in blind individuals, could first, substantiate the causal role of the affected regions in the reorganized functions, and second, provide interesting insight during and after rehabilitation. This could answer questions such as: 1) in what way would damage to V1 impair language functioning? 2) would classical frontotemporal language regions be able to compensate for this impairment? and 3) if so, what are the time constants of this process?

4.5. Conclusion

What is the visual cortex precisely computing in the early blind? The short answer is that we do not know. However, we find ample evidence that it is involved in both auditory and tactile perceptual functions, commonly resolved in their respective associative sensory cortices, and high-order cognitive functions, commonly resolved in the prefrontal, temporal and parietal cortices. Moreover, influential theories link this functional reorganization to innate connectivity biases that push the system in a different direction when visual input is not present.

Future studies can help understanding the full extent of this reorganization and its exact contribution to computation in the brain. Consequently, this knowledge would shed light on the general principals governing cortical specialization in the brain.

References

Abboud S, Maidenbaum S, Dehaene S, Amedi A. 2015. A number-form area in the blind. Nat Commun. 6:6026.

Alary F, Duquette M, Goldstein R, Elaine Chapman C, Voss P, La Buissonnière-Ariza V, Lepore F. 2009. Tactile acuity in the blind: A closer look reveals superiority over the sighted in some but not all cutaneous tasks. Neuropsychologia. 47:2037–2043.

Alary F, Goldstein R, Duquette M, Chapman CE, Voss P, Lepore F. 2008. Tactile acuity in the blind: a psychophysical study using a two-dimensional angle discrimination task. Exp Brain Res. 187:587–594.

Alcauter S, Lin W, Smith JK, Short SJ, Goldman BD, Reznick JS, Gilmore JH, Gao W. 2014. Development of Thalamocortical Connectivity during Infancy and Its Cognitive Correlations. J Neurosci. 34:9067–9075.

Alho K, Kujala T, Paavilainen P, Summala H, Näätänen R. 1993. Auditory processing in visual brain areas of the early blind: evidence from event-related potentials. Electroencephalogr Clin Neurophysiol. 86:418–427.

Amedi A, Floel A, Knecht S, Zohary E, Cohen LG. 2004. Transcranial magnetic stimulation of the occipital pole interferes with verbal processing in blind subjects. Nat Neurosci. 7:1266–1270.

Amedi A, Raz N, Azulay H, Malach R, Zohary E. 2010. Cortical activity during tactile exploration of objects in blind and sighted humans. Restor Neurol Neurosci. 28:143–156.

Amedi A, Raz N, Pianka P, Malach R, Zohary E. 2003. Early “visual” cortex activation correlates with superior verbal memory performance in the blind. Nat Neurosci. 6:758–766.

Amedi A, Stern WM, Camprodon JA, Bermpohl F, Merabet L, Rotman S, Hemond C, Meijer P, Pascual-Leone A. 2007. Shape conveyed by visual-to-auditory sensory substitution activates the lateral occipital complex. Nat Neurosci. 10:687–689.

Amemiya T, Beck B, Walsh V, Gomi H, Haggard P. 2017. Visual area V5/hMT+ contributes to perception of tactile motion direction: a TMS study. Sci Rep. 7:40937.

Anticevic A, Dierker DL, Gillespie SK, Repovs G, Csernansky JG, Van Essen DC, Barch DM. 2008. Comparing surface-based and volume-based analyses of functional neuroimaging data in patients with schizophrenia. NeuroImage. 41:835–848.

Armstrong BA, Neville HJ, Hillyard SA, Mitchell TV. 2002. Auditory deprivation affects processing of motion, but not color. Cogn Brain Res. 14:422–434.

Arnaud L, Sato M, Ménard L, Gracco VL. 2013. Repetition Suppression for Speech Processing in the Associative Occipital and Parietal Cortex of Congenitally Blind Adults. PLoS ONE. 8:e64553.

Bach-y-Rita P, Collins CC, Saunders FA, White B, Scadden L. 1969. Vision substitution by tactile image projection. Nature. 221:963–964.

Basser PJ, Pajevic S, Pierpaoli C, Duda J, Aldroubi A. 2000. In vivo fiber tractography using DT-MRI data. Magn Reson Med. 44:625–632.

Bauer C, Yazzolino L, Hirsch G, Cattaneo Z, Vecchi T, Merabet LB. 2015. Neural correlates associated with superior tactile symmetry perception in the early blind. Cortex. 63:104–117.

Bavelier D, Neville HJ. 2002. Cross-modal plasticity: where and how? Nat Rev Neurosci. 3:443–452.

Beaulieu-Lefebvre M, Schneider FC, Kupers R, Ptito M. 2011. Odor perception and odor awareness in congenital blindness. Brain Res Bull. 84:206–209.

Bedny M. 2017. Evidence from Blindness for a Cognitively Pluripotent Cortex. Trends Cogn Sci. 21:637–648.

Bedny M, Pascual-Leone A, Dodell-Feder D, Fedorenko E, Saxe R. 2011. Language processing in the occipital cortex of congenitally blind adults. Proc Natl Acad Sci. 108:4429–4434.

Bedny M, Richardson H, Saxe R. 2015. “Visual” Cortex Responds to Spoken Language in Blind Children. J Neurosci Off J Soc Neurosci. 35:11674–11681.

Beisteiner R, Windischberger C, Geißler A, Gartus A, Uhl F, Moser E, Deecke L, Lanzenberger R. 2015. FMRI correlates of different components of Braille reading by the blind. Neurol Psychiatry Brain Res. 21:137–145.

Bi Y, Wang X, Caramazza A. 2016. Object Domain and Modality in the Ventral Visual Pathway. Trends Cogn Sci. 20:282–290.

Binder JR, Desai RH. 2011. The neurobiology of semantic memory. Trends Cogn Sci. 15:527–536.

Bliss I, Kujala T, Hämäläinen H. 2004. Comparison of blind and sighted participants’ performance in a letter recognition working memory task. Cogn Brain Res. 18:273–277.

Bock AS, Fine I. 2014. Anatomical and functional plasticity in early blind individuals and the mixture of experts architecture. Front Hum Neurosci. 8.

Bock AS, Saenz M, Tungaraza R, Boynton GM, Bridge H, Fine I. 2013. Visual callosal topography in the absence of retinal input. NeuroImage. 81:325–334.

Boroujeni FM, Heidari F, Rouzbahani M, Kamali M. 2017. Comparison of auditory stream segregation in sighted and early blind individuals. Neurosci Lett. 638:218–221.

Bouhali F, Thiebaut de Schotten M, Pinel P, Poupon C, Mangin J-F, Dehaene S, Cohen L. 2014. Anatomical connections of the visual word form area. J Neurosci Off J Soc Neurosci. 34:15402–15414.

Bourgeois JP, Rakic P. 1993. Changes of synaptic density in the primary visual cortex of the macaque monkey from fetal to adult stage. J Neurosci Off J Soc Neurosci. 13:2801–2820.

Bouton S, Chambon V, Tyrand R, Guggisberg AG, Seeck M, Karkar S, van de Ville D, Giraud A-L. 2018. Focal versus distributed temporal cortex activity for speech sound category assignment. Proc Natl Acad Sci. 115:E1299–E1308.

Braddick OJ, O’Brien JM, Wattam-Bell J, Atkinson J, Hartley T, Turner R. 2001. Brain areas sensitive to coherent visual motion. Perception. 30:61–72.

Büchel C. 2003. Cortical hierarchy turned on its head. Nat Neurosci. 6:657–658.

Burton H, Diamond JB, McDermott KB. 2003. Dissociating Cortical Regions Activated by Semantic and Phonological Tasks: A fMRI Study in Blind and Sighted People. J Neurophysiol. 90:1965–1982.

Burton H, McLaren DG, Sinclair RJ. 2006. Reading embossed capital letters: An fMRI study in blind and sighted individuals. Hum Brain Mapp. 27:325–339.

Burton H, Sinclair RJ, Agato A. 2012. Recognition memory for Braille or spoken words: an fMRI study in early blind. Brain Res. 1438:22–34.

Burton H, Sinclair RJ, Dixit S. 2010. Working memory for vibrotactile frequencies: comparison of cortical activity in blind and sighted individuals. Hum Brain Mapp. 31:1686–1701.

Burton H, Sinclair RJ, McLaren DG. 2004. Cortical activity to vibrotactile stimulation: An fMRI study in blind and sighted individuals. Hum Brain Mapp. 23:210–228.

Burton H, Snyder AZ, Diamond JB, Raichle ME. 2002. Adaptive changes in early and late blind: a FMRI study of verb generation to heard nouns. J Neurophysiol. 88:3359–3371.

Burton H, Snyder AZ, Raichle ME. 2014. Resting state functional connectivity in early blind humans. Front Syst Neurosci. 8.

Butt OH, Benson NC, Datta R, Aguirre GK. 2013. The fine-scale functional correlation of striate cortex in sighted and blind people. J Neurosci Off J Soc Neurosci. 33:16209–16219.

Buzsáki G. 2006. Rhythms of the brain. Oxford: Oxford Univ. Press.

Buzsaki G, Draguhn A. 2004. Neuronal Oscillations in Cortical Networks. Science. 304:1926–1929.

Buzsáki G, Logothetis N, Singer W. 2013. Scaling Brain Size, Keeping Timing: Evolutionary Preservation of Brain Rhythms. Neuron. 80:751–764.

Castronovo J, Delvenne J-F. 2013. Superior numerical abilities following early visual deprivation. Cortex. 49:1435–1440.

Castronovo J, Seron X. 2007a. Numerical estimation in blind subjects: Evidence of the impact of blindness and its following experience. J Exp Psychol Hum Percept Perform. 33:1089–1106.

Castronovo J, Seron X. 2007b. Semantic numerical representation in blind subjects: The role of vision in the spatial format of the mental number line. Q J Exp Psychol. 60:101–119.

Cohen AL, Fair DA, Dosenbach NUF, Miezin FM, Dierker D, Van Essen DC, Schlaggar BL, Petersen SE. 2008. Defining functional areas in individual human brains using resting functional connectivity MRI. NeuroImage. 41:45–57.

Cohen L. 2002. Language-specific tuning of visual cortex? Functional properties of the Visual Word Form Area. Brain. 125:1054–1069.

Cohen LG, Celnik P, Pascual-Leone A, Corwell B, Falz L, Dambrosia J, Honda M, Sadato N, Gerloff C, Catalá MD, Hallett M. 1997. Functional relevance of cross-modal plasticity in blind humans. Nature. 389:180–183.

Collignon O, Davare M, Olivier E, De Volder AG. 2009. Reorganisation of the Right Occipito-Parietal Stream for Auditory Spatial Processing in Early Blind Humans. A Transcranial Magnetic Stimulation Study. Brain Topogr. 21:232–240.

Collignon O, Renier L, Bruyer R, Tranduy D, Veraart C. 2006. Improved selective and divided spatial attention in early blind subjects. Brain Res. 1075:175–182.

Collignon O, Vandewalle G, Voss P, Albouy G, Charbonneau G, Lassonde M, Lepore F. 2011. Functional specialization for auditory-spatial processing in the occipital cortex of congenitally blind humans. Proc Natl Acad Sci. 108:4435–4440.

Çomoğlu Ş, Orhan KS, Kocaman SÜ, Çelik M, Keleş N, Değer K. 2015. Olfactory Function Assessment of Blind Subjects Using the Sniffin' Sticks Test. Otolaryngol--Head Neck Surg Off J Am Acad Otolaryngol-Head Neck Surg. 153:286–290.

Cornell Kärnekull S, Arshamian A, Nilsson ME, Larsson M. 2016. From Perception to Metacognition: Auditory and Olfactory Functions in Early Blind, Late Blind, and Sighted Individuals. Front Psychol. 7.

Crollen V, Mahe R, Collignon O, Seron X. 2011. The role of vision in the development of finger–number interactions: Finger-counting and finger-montring in blind children. J Exp Child Psychol. 109:525–539.

Cuevas I, Plaza P, Rombaux P, Collignon O, De Volder AG, Renier L. 2010. Do people who became blind early in life develop a better sense of smell? A psychophysical study. J Vis Impair Blind. 104:369.

Cuevas I, Plaza P, Rombaux P, De Volder AG, Renier L. 2009. Odour discrimination and identification are improved in early blindness. Neuropsychologia. 47:3079–3083.

Damoiseaux JS, Greicius MD. 2009. Greater than the sum of its parts: a review of studies combining structural connectivity and resting-state functional connectivity. Brain Struct Funct. 213:525–533.

Deen B, Saxe R, Bedny M. 2015a. Occipital Cortex of Blind Individuals Is Functionally Coupled with Executive Control Areas of Frontal Cortex. J Cogn Neurosci. 27:1633–1647.

Deen B, Saxe R, Bedny M. 2015b. Occipital cortex of blind individuals is functionally coupled with executive control areas of frontal cortex. J Cogn Neurosci. 27:1633–1647.

Degenaar M. 1996. Molyneux's problem: three centuries of discussion on the perception of forms. Springer Science & Business Media.

Dehaene S, Cohen L. 2007. Cultural recycling of cortical maps. Neuron. 56:384–398.

Dehay C, Giroud P, Berland M, Killackey H, Kennedy H. 1996. Contribution of thalamic input to the specification of cytoarchitectonic cortical fields in the primate: effects of bilateral enucleation in the fetal monkey on the boundaries, dimensions, and gyrification of striate and extrastriate cortex. J Comp Neurol. 367:70–89.

Dietrich S, Hertrich I, Ackermann H. 2013. Ultra-fast speech comprehension in blind subjects engages primary visual cortex, fusiform gyrus, and pulvinar – a functional magnetic resonance imaging (fMRI) study. BMC Neurosci. 14:74.

Dormal G, Pelland M, Rezk M, Yakobov E, Lepore F, Collignon O. 2018. Functional Preference for Object Sounds and Voices in the Brain of Early Blind and Sighted Individuals. J Cogn Neurosci. 30:86–106.

Dormal G, Rezk M, Yakobov E, Lepore F, Collignon O. 2016. Auditory motion in the sighted and blind: Early visual deprivation triggers a large-scale imbalance between auditory and "visual" brain regions. NeuroImage. 134:630–644.

Dormal V, Crollen V, Baumans C, Lepore F, Collignon O. 2016. Early but not late blindness leads to enhanced arithmetic and working memory abilities. Cortex. 83:212–221.

Doucet M-E, Guillemot J-P, Lassonde M, Gagnð J-P, Leclerc C, Lepore F. 2005. Blind subjects process auditory spectral cues more efficiently than sighted individuals. Exp Brain Res. 160:194–202.

Eckert MA, Kamdar NV, Chang CE, Beckmann CF, Greicius MD, Menon V. 2008. A cross-modal system linking primary auditory and visual cortices: Evidence from intrinsic fMRI connectivity analysis. Hum Brain Mapp. 29:848–857.

Egner T, Hirsch J. 2005. Cognitive control mechanisms resolve conflict through cortical amplification of task-relevant information. Nat Neurosci. 8:1784–1790.

Fitzgibbon S, Andersson J, Harrison S, Robinson E, Bozek J, Makropoulos A, Bastiani M, Griffanti L, Wright R, Schuh A. 2017. The developing Human Connectome Project automated functional pre-processing pipeline for neonates. In: 23rd Annual Meeting of the Organization for Human Brain Mapping.

Föcker J, Best A, Hölig C, Röder B. 2012. The superiority in voice processing of the blind arises from neural plasticity at sensory processing stages. Neuropsychologia. 50:2056–2067.

Forkel SJ, Thiebaut de Schotten M, Kawadler JM, Dell'Acqua F, Danek A, Catani M. 2014. The anatomy of fronto-occipital connections from early blunt dissections to contemporary tractography. Cortex. 56:73–84.

Foster A, Gilbert C. 1992. Epidemiology of childhood blindness. Eye. 6:173–176.

Fox MD, Raichle ME. 2007. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nat Rev Neurosci. 8:700–711.

Gagnon L, Kupers R, Ptito M. 2013. Reduced Taste Sensitivity in Congenital Blindness. Chem Senses. 38:509–517.

Gilmore JH, Knickmeyer RC, Gao W. 2018. Imaging structural and functional brain development in early childhood. Nat Rev Neurosci. 19:123–137.

Gizewski E., Gasser T, de Greiff A, Boehm A, Forsting M. 2003. Cross-modal plasticity for sensory and motor activation patterns in blind subjects. NeuroImage. 19:968–975.

Glyn V, Lim VK, Hamm JP, Mathur A, Hughes B. 2015. Behavioural and electrophysiological effects related to semantic violations during braille reading. Neuropsychologia. 77:298–312.

Goldreich D, Kanics IM. 2003. Tactile acuity is enhanced in blindness. J Neurosci Off J Soc Neurosci. 23:3439–3445.

Gomez J, Pestilli F, Witthoft N, Golarai G, Liberman A, Poltoratski S, Yoon J, Grill-Spector K. 2015. Functionally Defined White Matter Reveals Segregated Pathways in Human Ventral Temporal Cortex Associated with Category-Specific Processing. Neuron. 85:216–227.

Gordon-Salant S, Friedman SA. 2011. Recognition of rapid speech by blind and sighted older adults. J Speech Lang Hear Res JSLHR. 54:622–631.

Gori M, Sandini G, Martinoli C, Burr DC. 2014. Impairment of auditory spatial localization in congenitally blind human subjects. Brain. 137:288–293.

Gougoux F, Belin P, Voss P, Lepore F, Lassonde M, Zatorre RJ. 2009. Voice perception in blind persons: A functional magnetic resonance imaging study. Neuropsychologia. 47:2967–2974.

Gougoux F, Lepore F, Lassonde M, Voss P, Zatorre RJ, Belin P. 2004. Neuropsychology: pitch discrimination in the early blind. Nature. 430:309.

Gougoux F, Zatorre RJ, Lassonde M, Voss P, Lepore F. 2005. A functional neuroimaging study of sound localization: visual cortex activity predicts performance in early-blind individuals. PLoS Biol. 3:e27.

Grant AC, Thiagarajah MC, Sathian K. 2000. Tactile perception in blind Braille readers: A psychophysical study of acuity and hyperacuity using gratings and dot patterns. Percept Psychophys. 62:301–312.

Grill-Spector K, Weiner KS. 2014. The functional architecture of the ventral temporal cortex and its role in categorization. Nat Rev Neurosci. 15:536–548.

Gurtubay-Antolin A, Rodríguez-Fornells A. 2017. Neurophysiological evidence for enhanced tactile acuity in early blindness in some but not all haptic tasks. NeuroImage. 162:23–31.

Hamilton R, Keenan JP, Catala M, Pascual-Leone A. 2000. Alexia for Braille following bilateral occipital stroke in an early blind woman. Neuroreport. 11:237–240.

Hamilton RH, Pascual-Leone A. 1998. Cortical plasticity associated with Braille learning. Trends Cogn Sci. 2:168–174.

Hamilton RH, Pascual-Leone A, Schlaug G. 2004. Absolute pitch in blind musicians. Neuroreport. 15:803–806.

Hannagan T, Amedi A, Cohen L, Dehaene-Lambertz G, Dehaene S. 2015. Origins of the specialization for letters and numbers in ventral occipitotemporal cortex. Trends Cogn Sci. 19:374–382.

Hawellek DJ, Schepers IM, Roeder B, Engel AK, Siegel M, Hipp JF. 2013. Altered Intrinsic Neuronal Interactions in the Visual Cortex of the Blind. J Neurosci. 33:17072–17080.

Haxby JV, Grady CL, Horwitz B, Ungerleider LG, Mishkin M, Carson RE, Herscovitch P, Schapiro MB, Rapoport SI. 1991. Dissociation of object and spatial visual processing pathways in human extrastriate cortex. Proc Natl Acad Sci U S A. 88:1621–1625.

He C, Peelen MV, Han Z, Lin N, Caramazza A, Bi Y. 2013. Selectivity for large nonmanipulable objects in scene-selective visual cortex does not require visual experience. NeuroImage. 79:1–9.

Heller MA. 1989. Texture perception in sighted and blind observers. Percept Psychophys. 45:49–54.

Hipp JF, Hawellek DJ, Corbetta M, Siegel M, Engel AK. 2012. Large-scale cortical correlation structure of spontaneous oscillatory activity. Nat Neurosci. 15:884–890.

Hölig C, Föcker J, Best A, Röder B, Büchel C. 2014. Brain systems mediating voice identity processing in blind humans: Voice Identity Processing in Blind Humans. Hum Brain Mapp. 35:4607–4619.

Hötting K, Röder B. 2009. Auditory and auditory-tactile processing in congenitally blind humans. Hear Res. 258:165–174.

Hugdahl K, Ek M, Takio F, Rintee T, Tuomainen J, Haarala C, Hämäläinen H. 2004. Blind individuals show enhanced perceptual and attentional sensitivity for identification of speech sounds. Cogn Brain Res. 19:28–32.

Hughes E, Grande LC, Murgasova M, Hutter J, Price A, Gomes AS. 2017. The Developing Human Connectome: announcing the first release of open access neonatal brain imaging. In: 23rd Annual Meeting of the Organization for Human Brain Mapping.

Hutchison RM, Culham JC, Everling S, Flanagan JR, Gallivan JP. 2014. Distinct and distributed functional connectivity patterns across cortex reflect the domain-specific constraints of object, face, scene, body, and tool category-selective modules in the ventral visual pathway. NeuroImage. 96:216–236.

Jabaudon D. 2017. Fate and freedom in developing neocortical circuits. Nat Commun. 8:16042.

Jiang F, Stecker GC, Fine I. 2014. Auditory motion processing after early blindness. J Vis. 14:4.

Kanjlia S, Lane C, Feigenson L, Bedny M. 2016. Absence of visual experience modifies the neural basis of numerical thinking. Proc Natl Acad Sci. 113:11172–11177.

Kim JS, Kanjlia S, Merabet LB, Bedny M. 2017. Development of the Visual Word Form Area Requires Visual Experience: Evidence from Blind Braille Readers. J Neurosci. 37:11495–11504.

King AJ. 2015. Crossmodal plasticity and hearing capabilities following blindness. Cell Tissue Res. 361:295–300.

Kolarik AJ, Cirstea S, Pardhan S. 2013. Evidence for enhanced discrimination of virtual auditory distance among blind listeners using level and direct-to-reverberant cues. Exp Brain Res. 224:623–633.

Kolarik AJ, Cirstea S, Pardhan S, Moore BCJ. 2014. A summary of research investigating echolocation abilities of blind and sighted humans. Hear Res. 310:60–68.

Kolarik AJ, Moore BCJ, Zahorik P, Cirstea S, Pardhan S. 2016. Auditory distance perception in humans: a review of cues, development, neuronal bases, and effects of sensory loss. Atten Percept Psychophys. 78:373–395.

Kriegseis A, Hennighausen E, Rösler F, Röder B. 2006. Reduced EEG alpha activity over parieto-occipital brain areas in congenitally blind adults. Clin Neurophysiol. 117:1560–1573.

Kujala T, Alho K, Paavilainen P, Summala H, Näätänen R. 1992. Neural plasticity in processing of sound location by the early blind: an event-related potential study. Electroencephalogr Clin Neurophysiol. 84:469–472.

Kujala T, Huotilainen M, Sinkkonen J, Ahonen AI, Alho K, Hämäläinen MS, Ilmoniemi RJ, Kajola M, Knuutila JE, Lavikainen J. 1995. Visual cortex activation in blind humans during sound discrimination. Neurosci Lett. 183:143–146.

Kutas M, Federmeier KD. 2011. Thirty Years and Counting: Finding Meaning in the N400 Component of the Event-Related Brain Potential (ERP). Annu Rev Psychol. 62:621–647.

Lai H-H, Chen Y-C. 2006. A study on the blind's sensory ability. Int J Ind Ergon. 36:565–570.

Lane C, Kanjlia S, Omaki A, Bedny M. 2015. "Visual" Cortex of Congenitally Blind Adults Responds to Syntactic Movement. J Neurosci Off J Soc Neurosci. 35:12859–12868.

Lane C, Kanjlia S, Richardson H, Fulton A, Omaki A, Bedny M. 2017. Reduced Left Lateralization of Language in Congenitally Blind Individuals. J Cogn Neurosci. 29:65–78.

Leclerc C, Saint-Amour D, Lavoie ME, Lassonde M, Lepore F. 2000. Brain functional reorganization in early blind humans revealed by auditory event-related potentials. Neuroreport. 11:545–550.

Lerens E, Renier L. 2014. Does visual experience influence the spatial distribution of auditory attention? Acta Psychol (Amst). 146:58–62.

Lessard N, Paré M, Lepore F, Lassonde M. 1998. Early-blind human subjects localize sound sources better than sighted subjects. Nature. 395:278–280.

Lewald J. 2002. Vertical sound localization in blind humans. Neuropsychologia. 40:1868–1872.

Lewis LB, Saenz M, Fine I. 2010. Mechanisms of cross-modal plasticity in early-blind subjects. J Neurophysiol. 104:2995–3008.

Liotti M, Ryder K, Woldorff MG. 1998. Auditory attention in the congenitally blind: where, when and what gets reorganized? Neuroreport. 9:1007–1012.

Liu Y, Yu C, Liang M, Li J, Tian L, Zhou Y, Qin W, Li K, Jiang T. 2007. Whole brain functional connectivity in the early blind. Brain J Neurol. 130:2085–2096.

Lomber SG, Meredith MA, Kral A. 2010. Cross-modal plasticity in specific auditory cortices underlies visual compensations in the deaf. Nat Neurosci. 13:1421–1427.

Lomber SG, Payne BR, Horel JA. 1999. The cryoloop: an adaptable reversible cooling deactivation method for behavioral or electrophysiological assessment of neural function. J Neurosci Methods. 86:179–194.

Luo H, Poeppel D. 2007. Phase Patterns of Neuronal Responses Reliably Discriminate Speech in Human Auditory Cortex. Neuron. 54:1001–1010.

Macé MJ-M, Dramas F, Jouffrais C. 2012. Reaching to Sound Accuracy in the Peri-personal Space of Blind and Sighted Humans. In: Miesenberger K,, Karshmer A,, Penaz P,, Zagler W, editors. Computers Helping People with Special Needs. Berlin, Heidelberg: Springer Berlin Heidelberg. p. 636–643.

Mahon BZ, Anzellotti S, Schwarzbach J, Zampini M, Caramazza A. 2009. Category-Specific Organization in the Human Brain Does Not Require Visual Experience. Neuron. 63:397–405.

Mahon BZ, Caramazza A. 2011. What drives the organization of object knowledge in the brain? Trends Cogn Sci. 15:97–103.

Malach R, Reppas JB, Benson RR, Kwong KK, Jiang H, Kennedy WA, Ledden PJ, Brady TJ, Rosen BR, Tootell RB. 1995. Object-related activity revealed by functional magnetic resonance imaging in human occipital cortex. Proc Natl Acad Sci. 92:8135–8139.

Matteau I, Kupers R, Ricciardi E, Pietrini P, Ptito M. 2010. Beyond visual, aural and haptic movement perception: hMT+ is activated by electrotactile motion stimulation of the tongue in sighted and in congenitally blind individuals. Brain Res Bull. 82:264–270.

Merabet LB, Hamilton R, Schlaug G, Swisher JD, Kiriakopoulos ET, Pitskel NB, Kauffman T, Pascual-Leone A. 2008. Rapid and Reversible Recruitment of Early Visual Cortex for Touch. PLoS ONE. 3:e3046.

Meredith MA, Lomber SG. 2011. Somatosensory and visual crossmodal plasticity in the anterior auditory field of early-deaf cats. Hear Res. 280:38–47.

Morgan M. 1999. Sensory perception: Supernormal hearing in the blind? Curr Biol. 9:R53–R54.

Muchnik C, Efrati M, Nemeth E, Malin M, Hildesheimer M. 1991. Central auditory skills in blind and sighted subjects. Scand Audiol. 20:19–23.

Murphy C, Cain WS. 1986. Odor identification: The blind are better. Physiol Behav. 37:177–180.

New B, Pallier C, Brysbaert M, Ferrand L. 2004. Lexique 2: a new French lexical database. Behav Res Methods Instrum Comput J Psychon Soc Inc. 36:516–524.

Niemeyer W, Starlinger I. 1981. Do the Blind Hear Better? Investigations on Auditory Processing in Congenital or Early Acquired Blindness II. Central Functions. Audiology. 20:510–515.

Occelli V, Lacey S, Stephens C, Merabet LB, Sathian K. 2017. Enhanced verbal abilities in the congenitally blind. Exp Brain Res. 235:1709–1718.

Ockley S. 1708. The improvement of human reason : exhibited in the life of Hai ebn Yokdhan. London: Printed and sold by E. Powell.

Ofan RH, Zohary E. 2007. Visual cortex activation in bilingual blind individuals during use of native and second language. Cereb Cortex N Y N 1991. 17:1249–1259.

Osher DE, Saxe RR, Koldewyn K, Gabrieli JDE, Kanwisher N, Saygin ZM. 2016. Structural Connectivity Fingerprints Predict Cortical Selectivity for Multiple Visual Categories across Cortex. Cereb Cortex. 26:1668–1683.

Pascual-Leone A, Hamilton R. 2001. The metamodal organization of the brain. Prog Brain Res. 134:427–445.

Pasqualotto A, Lam JSY, Proulx MJ. 2013. Congenital blindness improves semantic and episodic memory. Behav Brain Res. 244:162–165.

Peelen MV, Bracci S, Lu X, He C, Caramazza A, Bi Y. 2013. Tool Selectivity in Left Occipitotemporal Cortex Develops without Vision. J Cogn Neurosci. 25:1225–1234.

Peelen MV, Downing PE. 2017. Category selectivity in human visual cortex: Beyond visual object recognition. Neuropsychologia. 105:177–183.

Pietrini P, Furey ML, Ricciardi E, Gobbini MI, Wu W-HC, Cohen L, Guazzelli M, Haxby JV. 2004. Beyond sensory images: Object-based representation in the human ventral pathway. Proc Natl Acad Sci U S A. 101:5658–5663.

Pigeon C, Marin-Lamellet C. 2015. Evaluation of the attentional capacities and working memory of early and late blind persons. Acta Psychol (Amst). 155:1–7.

Pishnamazi M, Nojaba Y, Ganjgahi H, Amousoltani A, Oghabian MA. 2016. Neural correlates of audiotactile phonetic processing in early-blind readers: an fMRI study. Exp Brain Res. 234:1263–1277.

Prather SC, Votaw JR, Sathian K. 2004. Task-specific recruitment of dorsal and ventral visual areas during tactile perception. Neuropsychologia. 42:1079–1087.

Ptito M, Fumal A, de Noordhout AM, Schoenen J, Gjedde A, Kupers R. 2008. TMS of the occipital cortex induces tactile sensations in the fingers of blind Braille readers. Exp Brain Res. 184:193–200.

Ptito M, Moesgaard SM, Gjedde A, Kupers R. 2005. Cross-modal plasticity revealed by electrotactile stimulation of the tongue in the congenitally blind. Brain J Neurol. 128:606–614.

Ptito M, Schneider FCG, Paulson OB, Kupers R. 2008. Alterations of the visual pathways in congenital blindness. Exp Brain Res. 187:41–49.

Qin W, Liu Y, Jiang T, Yu C. 2013. The development of visual areas depends differently on visual experience. PloS One. 8:e53784.

Rakic P, Suñer I, Williams RW. 1991. A novel cytoarchitectonic area induced experimentally within the primate visual cortex. Proc Natl Acad Sci U S A. 88:2083–2087.

Rauschecker JP. 1995. Compensatory plasticity and sensory substitution in the cerebral cortex. Trends Neurosci. 18:36–43.

Rauschecker JP, Korte M. 1993. Auditory compensation for early blindness in cat cerebral cortex. J Neurosci Off J Soc Neurosci. 13:4538–4548.

Raz N, Amedi A, Zohary E. 2005. V1 Activation in Congenitally Blind Humans is Associated with Episodic Retrieval. Cereb Cortex. 15:1459–1468.

Raz N, Striem E, Pundak G, Orlov T, Zohary E. 2007. Superior Serial Memory in the Blind: A Case of Cognitive Compensatory Adjustment. Curr Biol. 17:1129–1133.

Reich L, Szwed M, Cohen L, Amedi A. 2011. A ventral visual stream reading center independent of visual experience. Curr Biol CB. 21:363–368.

Renier LA, Anurova I, De Volder AG, Carlson S, VanMeter J, Rauschecker JP. 2010. Preserved Functional Specialization for Spatial Processing in the Middle Occipital Gyrus of the Early Blind. Neuron. 68:138–148.

Ricciardi E, Vanello N, Sani L, Gentili C, Scilingo EP, Landini L, Guazzelli M, Bicchi A, Haxby JV, Pietrini P. 2007. The effect of visual experience on the development of functional architecture in hMT+. Cereb Cortex N Y N 1991. 17:2933–2939.

Röder B, Rösler F. 2003. Memory for environmental sounds in sighted, congenitally blind and late blind adults: evidence for cross-modal compensation. Int J Psychophysiol. 50:27–39.

Röder B, Rösler F, Hennighausen E, Näcker F. 1996. Event-related potentials during auditory and somatosensory discrimination in sighted and blind human subjects. Brain Res Cogn Brain Res. 4:77–93.

Röder B, Rösler F, Neville HJ. 2000. Event-related potentials during auditory language processing in congenitally blind and sighted people. Neuropsychologia. 38:1482–1502.

Röder B, Rösler F, Neville HJ. 2001. Auditory memory in congenitally blind adults: a behavioral-electrophysiological investigation. Cogn Brain Res. 11:289–303.

Röder B, Teder-Sälejärvi W, Sterr A, Rösler F, Hillyard SA, Neville HJ. 1999. Improved auditory spatial tuning in blind humans. Nature. 400:162–166.

Rokem A, Ahissar M. 2009. Interactions of cognitive and auditory abilities in congenitally blind individuals. Neuropsychologia. 47:843–848.

Rombaux P, Huart C, De Volder AG, Cuevas I, Renier L, Duprez T, Grandin C. 2010. Increased olfactory bulb volume and olfactory function in early blind subjects: NeuroReport. 21:1069–1073.

Rosenbluth R, Grossman ES, Kaitz M. 2000. Performance of Early-Blind and Sighted Children on Olfactory Tasks. Perception. 29:101–110.

Rösler F, Röder B, Heil M, Hennighausen E. 1993. Topographic differences of slow event-related brain potentials in blind and sighted adult human subjects during haptic mental rotation. Cogn Brain Res. 1:145–159.

Sadato N, Pascual-Leone A, Grafman J, Ibañez V, Deiber MP, Dold G, Hallett M. 1996. Activation of the primary visual cortex by Braille reading in blind subjects. Nature. 380:526–528.

Sathian K, Stilla R. 2010. Cross-modal plasticity of tactile perception in blindness. Restor Neurol Neurosci. 271–281.

Saygin ZM, Osher DE, Koldewyn K, Reynolds G, Gabrieli JDE, Saxe RR. 2012. Anatomical connectivity patterns predict face selectivity in the fusiform gyrus. Nat Neurosci. 15:321–327.

Saygin ZM, Osher DE, Norton ES, Youssoufian DA, Beach SD, Feather J, Gaab N, Gabrieli JDE, Kanwisher N. 2016. Connectivity precedes function in the development of the visual word form area. Nat Neurosci. 19:1250–1255.

Schepers IM, Hipp JF, Schneider TR, Röder B, Engel AK. 2012. Functionally specific oscillatory activity correlates between visual and auditory cortex in the blind. Brain. 135:922–934.

Schinazi VR, Thrash T, Chebat D-R. 2016. Spatial navigation by congenitally blind individuals: Spatial navigation by congenitally blind individuals. Wiley Interdiscip Rev Cogn Sci. 7:37–58.

Serag A, Aljabar P, Ball G, Counsell SJ, Boardman JP, Rutherford MA, Edwards AD, Hajnal JV, Rueckert D. 2012. Construction of a consistent high-definition spatio-temporal atlas of the developing brain using adaptive kernel regression. NeuroImage. 59:2255–2265.

Shimony JS, Burton H, Epstein AA, McLaren DG, Sun SW, Snyder AZ. 2006. Diffusion Tensor Imaging Reveals White Matter Reorganization in Early Blind Humans. Cereb Cortex. 16:1653–1661.

Shum J, Hermes D, Foster BL, Dastjerdi M, Rangarajan V, Winawer J, Miller KJ, Parvizi J. 2013. A Brain Area for Visual Numerals. J Neurosci. 33:6709–6715.

Siegel M, Donner TH, Engel AK. 2012. Spectral fingerprints of large-scale neuronal interactions. Nat Rev Neurosci. 13:121–134.

Sinclair RJ, Dixit S, Burton H. 2011. Recognition memory for vibrotactile rhythms: an fMRI study in blind and sighted individuals. Somatosens Mot Res. 28:48–62.

Smith RS, Doty RL, Burlingame GK, McKeown DA. 1993. Smell and taste function in the visually impaired. Percept Psychophys. 54:649–655.

Stevens AA, Snodgrass M, Schwartz D, Weaver K. 2007. Preparatory Activity in Occipital Cortex in Early Blind Humans Predicts Auditory Perceptual Performance. J Neurosci. 27:10734–10741.

Stevens AA, Weaver K. 2005. Auditory perceptual consolidation in early-onset blindness. Neuropsychologia. 43:1901–1910.

Stevens AA, Weaver KE. 2009. Functional characteristics of auditory cortex in the blind. Behav Brain Res. 196:134–138.

Stevens JC, Foulke E, Patterson MQ. 1996. Tactile acuity, aging, and braille reading in long-term blindness. J Exp Psychol Appl. 2:91–106.

Stilla R, Hanna R, Hu X, Mariola E, Deshpande G, Sathian K. 2008. Neural processing underlying tactile microspatial discrimination in the blind: A functional magnetic resonance imaging study. J Vis. 8:13–13.

Striem-Amit E, Amedi A. 2014. Visual cortex extrastriate body-selective area activation in congenitally blind people “seeing” by using sounds. Curr Biol CB. 24:687–692.

Striem-Amit E, Cohen L, Dehaene S, Amedi A. 2012. Reading with sounds: sensory substitution selectively activates the visual word form area in the blind. Neuron. 76:640–652.

Striem-Amit E, Ovadia-Caro S, Caramazza A, Margulies DS, Villringer A, Amedi A. 2015. Functional connectivity of visual cortex in the blind follows retinotopic organization principles. Brain J Neurol. 138:1679–1695.

Struiksma ME, Noordzij ML, Neggers SFW, Bosker WM, Postma A. 2011. Spatial language processing in the blind: evidence for a supramodal representation and cortical reorganization. PloS One. 6:e24253.

Sur M, Garraghty PE, Roe AW. 1988. Experimentally induced visual projections into auditory thalamus and cortex. Science. 242:1437–1441.

Szűcs D, Csépe V. 2005. The parietal distance effect appears in both the congenitally blind and matched sighted controls in an acoustic number comparison task. Neurosci Lett. 384:11–16.

Tagliazucchi E, Laufs H. 2014. Decoding Wakefulness Levels from Typical fMRI Resting-State Data Reveals Reliable Drifts between Wakefulness and Sleep. Neuron. 82:695–708.

Uhl F, Franzen P, Lindinger G, Lang W, Deecke L. 1991. On the functionality of the visually deprived occipital cortex in early blind persons. Neurosci Lett. 124:256–259.

Uhl F, Franzen P, Podreka I, Steiner M, Deecke L. 1993. Increased regional cerebral blood flow in inferior occipital cortex and cerebellum of early blind humans. Neurosci Lett. 150:162–164.

Van Ackeren MJ, Barbero FM, Mattioni S, Bottini R, Collignon O. 2018. Neuronal populations in the occipital cortex of the blind synchronize to the temporal dynamics of speech. eLife. 7.

Van Boven RW, Hamilton RH, Kauffman T, Keenan JP, Pascual-Leone A. 2000. Tactile spatial resolution in blind braille readers. Neurology. 54:2230–2236.

van den Hurk J, Van Baelen M, Op de Beeck HP. 2017. Development of visual category selectivity in ventral visual cortex does not require visual experience. Proc Natl Acad Sci. 114:E4501–E4510.

Van Essen DC. 2005. A Population-Average, Landmark- and Surface-based (PALS) atlas of human cerebral cortex. NeuroImage. 28:635–662.

Van Wanrooij MM, Van Opstal AJ. 2004. Contribution of head shadow and pinna cues to chronic monaural sound localization. J Neurosci Off J Soc Neurosci. 24:4163–4171.

Vercillo T, Burr D, Gori M. 2016. Early visual deprivation severely compromises the auditory sense of space in congenitally blind children. Dev Psychol. 52:847–853.

Voss P, Alary F, Lazzouni L, Chapman CE, Goldstein R, Bourgoin P, Lepore F. 2016. Crossmodal Processing of Haptic Inputs in Sighted and Blind Individuals. Front Syst Neurosci. 10.

Voss P, Gougoux F, Zatorre RJ, Lassonde M, Lepore F. 2008. Differential occipital responses in early- and late-blind individuals during a sound-source discrimination task. NeuroImage. 40:746–758.

Voss P, Lassonde M, Gougoux F, Fortin M, Guillemot J-P, Lepore F. 2004. Early- and Late-Onset Blind Individuals Show Supra-Normal Auditory Abilities in Far-Space. Curr Biol. 14:1734–1738.

Voss P, Lepore F, Gougoux F, Zatorre RJ. 2011. Relevance of Spectral Cues for Auditory Spatial Processing in the Occipital Cortex of the Blind. Front Psychol. 2.

Voss P, Tabry V, Zatorre RJ. 2015. Trade-Off in the Sound Localization Abilities of Early Blind Individuals between the Horizontal and Vertical Planes. J Neurosci. 35:6051–6056.

Voss P, Zatorre RJ. 2012. Organization and Reorganization of Sensory-Deprived Cortex. Curr Biol. 22:R168–R173.

Wakefield CE, Homewood J, Taylor AJ. 2004. Cognitive Compensations for Blindness in Children: An Investigation Using Odour Naming. Perception. 33:429–442.

Wan CY, Wood AG, Reutens DC, Wilson SJ. 2010. Early but not late-blindness leads to enhanced auditory perception. Neuropsychologia. 48:344–348.

Wanet MC, Veraart C. 1985. Processing of auditory information by the blind in spatial localization tasks. Percept Psychophys. 38:91–96.

Wanet-Defalque M-C, Veraart C, De Volder A, Metz R, Michel C, Dooms G, Goffinet A. 1988. High metabolic activity in the visual cortex of early blind human subjects. Brain Res. 446:369–373.

Wang D, Qin W, Liu Y, Zhang Y, Jiang T, Yu C. 2014. Altered resting-state network connectivity in congenital blind. Hum Brain Mapp. 35:2573–2581.

Wang X, He C, Peelen MV, Zhong S, Gong G, Caramazza A, Bi Y. 2017. Domain Selectivity in the Parahippocampal Gyrus Is Predicted by the Same Structural Connectivity Patterns in Blind and Sighted Individuals. J Neurosci. 37:4705–4716.

Wang X, Peelen MV, Han Z, He C, Caramazza A, Bi Y. 2015. How Visual Is the Visual Cortex? Comparing Connectional and Functional Fingerprints between Congenitally Blind and Sighted Individuals. J Neurosci Off J Soc Neurosci. 35:12545–12559.

Watkins KE, Cowey A, Alexander I, Filippini N, Kennedy JM, Smith SM, Ragge N, Bridge H. 2012. Language networks in anophthalmia: maintained hierarchy of processing in “visual” cortex. Brain J Neurol. 135:1566–1577.

Watkins KE, Shakespeare TJ, O’Donoghue MC, Alexander I, Ragge N, Cowey A, Bridge H. 2013. Early auditory processing in area V5/MT+ of the congenitally blind brain. J Neurosci Off J Soc Neurosci. 33:18242–18246.

Weaver KE, Stevens AA. 2007. Attention and sensory interactions within the occipital cortex in the early blind: an fMRI study. J Cogn Neurosci. 19:315–330.

Weeks R, Horwitz B, Aziz-Sultan A, Tian B, Wessinger CM, Cohen LG, Hallett M, Rauschecker JP. 2000. A positron emission tomographic study of auditory localization in the congenitally blind. J Neurosci Off J Soc Neurosci. 20:2664–2672.

Wiesel TN, Hubel DH. 1963. SINGLE-CELL RESPONSES IN STRIATE CORTEX OF KITTENS DEPRIVED OF VISION IN ONE EYE. J Neurophysiol. 26:1003–1017.

Withagen A, Kappers AML, Vervloed MPJ, Knoors H, Verhoeven L. 2012. Haptic object matching by blind and sighted adults and children. Acta Psychol (Amst). 139:261–271.

Withagen A, Kappers AML, Vervloed MPJ, Knoors H, Verhoeven L. 2013. Short term memory and working memory in blind versus sighted children. Res Dev Disabil. 34:2161–2172.

Wong M, Gnanakumaran V, Goldreich D. 2011. Tactile Spatial Acuity Enhancement in Blindness: Evidence for Experience-Dependent Mechanisms. J Neurosci. 31:7028–7037.

World Health Organization. 1992. The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines. World Health Organization.

Yu C, Liu Y, Li J, Zhou Y, Wang K, Tian L, Qin W, Jiang T, Li K. 2008. Altered functional connectivity of primary visual cortex in early blindness. Hum Brain Mapp. 29:533–543.

Zwiers M, Van Opstal A, Cruysberg J. 2001a. Two-dimensional sound-localization behavior of early-blind humans. Exp Brain Res. 140:206–222.

Zwiers MP, Van Opstal AJ, Cruysberg JR. 2001b. A spatial hearing deficit in early-blind humans. J Neurosci Off J Soc Neurosci. 21:RC142: 1-5.

List of figures

1. Introduction 1
Figure 1.1 – Tactile task conditions used by Stilla et al. (2008). 12
Figure 1.2 – Brain activation during controlled tactile tasks. 12
Figure 1.3 – Task overlap between the sighted and the blind. 15
Figure 1.4 – Modality-independent category selectivity in ventral occipitotemporal cortex. 18
Figure 1.5 – Visual activation by high-order cognitive functions. 24
2. Cognitive functions of the visual cortex in the blind 31
Figure 1 – Activation in the Blind and Sighted (conjunction and differences) 46
Figure 2 – Occipital seeds for the functional connectivity study 49
Figure 3 – Comparison of the functional connectivity between the blind and the sighted 50
Figure 4 – Unique connectivity fingerprints of the occipital seeds in the blind 51
Supplementary Figure 1 – Activation in the Blind and Sighted (separately) 57
Supplementary Figure 2 – Activation in the Blind and Sighted for the Initial condition (conjunction and differences). 58
Supplementary Figure 3 – Unique connectivity fingerprints for the occipital seeds in the sighted 59
Figure 2.2.1 – Unique functional connectivity in neonates and adults 67
3. Electrophysiological investigation of language 75
Figure 1 – Semantic decision task. 86
Figure 2 – Neural correlates of semantic processing. 87
Figure 3 – Neural correlates of semantic category discrimination. 89
Figure 4 – Single-trial decoding of semantic category discrimination. 90
Figure 5 – Cortical sources informative for semantic classification. 92
Figure 6 – Cross-subject generalization. 93
Supplementary Figure 1 – Semantic category time generalization. 98
Supplementary Figure 2 – Cortical sources informative for semantic classification at different time points. 99
Supplementary Figure 3 – Cortical sources informative for semantic classification at different time points. 100
Supplementary Figure 4 – Inter-subject variability. 101
Figure 3.2.1 – Phonemic category decoding. 106

Appendix A: A lateral-to-mesial organization of human ventral visual cortex at birth

A lateral-to-mesial organization of human ventral visual cortex at birth.

Barttfeld P[1,2*], Abboud S[4,5*], Lagercrantz H[6], Adén U[6], Padilla N[6]., Edwards AD[7], Cohen L[4,5], Sigman M[3], Dehaene S[1,8] & Dehaene-Lambertz G[1]

1- Cognitive Neuroimaging Unit, CEA DSV/I2BM, INSERM, Université Paris-Sud, Université Paris-Saclay, NeuroSpin Center, Gif-sur-Yvette, France
2- Laboratory of Experimental Psychology and Neuroscience (LPEN), INECO (Institute of Cognitive Neurology)
3- Universidad Torcuato Di Tella, Almirante Juan Saenz Valiente 1010, C1428BIJ Buenos Aires, Argentina.
4- INSERM, U 1127, Paris, F-75013, France.
5- Institut Du Cerveau Et De La Moelle Epinière, ICM, PICNIC Lab, Paris F-75013, France.
6- Department of Women's and Children's Health, Karolinska Institutet, 171 76 Stockholm , Sweden.
7- Centre for the Developing Brain, Division of Imaging Sciences & Biomedical Engineering, King's College London, London, UK.
8- Collège de France, 75005 Paris, France.

*These authors contributed equally to the work.

Abstract

In human adults, ventral extra-striate visual cortex contains a mosaic of functionally specialized areas, some responding preferentially to natural visual categories such as faces (fusiform face area) or places (parahippocampal place area) and others to cultural inventions such as written words and numbers (visual word form and number form areas). It has been hypothesized that this mosaic arises from innate biases in cortico-cortical connectivity. We tested this hypothesis by examining functional resting-state correlation at birth using fMRI data from full-term human newborns. The results revealed that ventral visual regions are functionally connected with their contra-lateral homologous regions and also exhibit distinct patterns of long-distance functional correlation with anterior associative regions. A mesial-to-lateral organization was observed, with the signal of the more lateral regions, including the sites of visual word and number form areas, exhibiting higher correlations with voxels of the prefrontal, inferior parietal and temporal cortices, including language areas. Finally, we observed hemispheric asymmetries in the functional correlation of key areas of the language network that may influence later adult hemispheric lateralization. We suggest that long-distance circuits present at birth constrain the subsequent functional differentiation of the ventral visual cortex.

Keywords

Neonates – brain - functional connectivity - language

Introduction

The human brain displays a remarkable consistency and reproducibility in its functional organization across individuals. This was first demonstrated in neuropsychological studies that mapped specific cognitive deficits to reproducible cortical lesion sites and more recently by brain-imaging research, which has revealed surprisingly similar functional subdivisions of the cortical surface across numerous individuals (Glasser et al., 2016; Huth, de Heer, Griffiths, Theunissen, & Gallant, 2016). Not only is this reproducible topological specialization evident in domains of evolutionary relevance, such as for the fusiform face area (FFA) and the parahippocampal place area (PPA) (Downing et al., 2006) but it also extends to cultural acquisitions such as reading. For example, the same region of the left fusiform gyrus, the visual form area (vWFA), is consistently activated whenever literate participants recognize written words, independently of case (Dehaene & Cohen, 2011), modality (Striem-Amit, Cohen, Dehaene, & Amedi, 2012) or the age of reading acquisition (Dehaene et al., 2010).

Such functional reproducibility suggests that cognitive processes are dependent on specific neural architectures (Hannagan, Amedi, Cohen, Dehaene-Lambertz, & Dehaene, 2015). Indeed, functional responses have been consistently related to specific micro-architectures (e.g. word and face-specific activations are observed in the regions FG2 and FG4, whereas places are activating FG1 and FG3, Weiner et al., 2016; Caspers et al., 2015), although the exact relation between a given cortical layer organization and a computational process are still poorly specified. Anatomical connectivity, by orchestrating local and distant synchrony, might also drive the functional role of an area. This "biased connectivity" hypothesis was recently supported by two studies showing that the precise locations of the FFA (Saygin et al., 2012) and VWFA (Saygin et al., 2016) can be predicted from their connections. The functional localization of the VWFA was predicted in 8-

year-old readers by the anatomical fiber tracking performed at the age of 5 before they learned to read (Saygin et al., 2016).

Because all main fiber tracts are already present in full-term human neonates (Dubois et al., 2014; Dubois et al., 2016; Kennedy et al., 2007; Kostovic & Judas, 2010; Marín-Padilla, 2011; Takahashi et al., 2011), in the present paper, we asked whether the initial connectome, present at birth, may explain at least some aspects of the subsequent functional specialization. We focused here on the masesial-to-lateral organization of ventral visual cortex. The ventral visual pathway comprises a succession of functional areas extending from mesial to lateral regions including the mesial place area (PPA), the face fusiform area (FFA), the visual word form area (VWFA), the number form area (NFA) and a more lateral area responding to tools and objects. Furthermore, distinct face and place responses are already present in 6-month-old infants (Deen et al, 2017). Here, we examined whether a particular connectivity pattern of these regions is already in place at birth.

To this aim, we relied on resting-state functional correlation, i.e. the synchronization of the BOLD responses across distant regions at rest due to the spontaneous co-activity of different nodes of the same network (Smith et al., 2013; Glasser et al., 2016; Raichle, 2015). Using this approach in full-term and even pre-term neonates, several studies have reported the presence of the main resting-state networks described in adults (Fransson et al., 2007; Fransson, Aden, Blennow, & Lagercrantz, 2011; Fransson et al., 2009; Doria et al., 2010; Smyser et al., 2010; Smyser, Snyder, & Neil, 2011) as also more specific connectivity, such as thalamocortical connectivity (Toulmin et al., 2015) or from multisensory areas (Sours et al., 2017). Our goal was to go beyond the whole-brain description and determine whether long-distance connections specifically arising from ventral visual areas already target distinct regions. We aimed to evaluate two contrasting theories

for the origins of adult functional specialization. The first of which, the "biased connectivity" hypothesis (Hannagan et al., 2015; Saygin et al., 2012) as explained above, predicts that mesial-to-lateral differences in functional correlation are already present at birth, in approximate correspondence to the functional mosaic later found in older children and adults. We then contrasted it to the latter hypothesis according to which brain connectivity is initially diffuse, over-abundant and largely isotropic and only becomes refined at a later stage during infancy and childhood through exposure to a given environment (Johnson, 2011; Elman et al., 1996).

The "biased connectivity" hypothesis makes specific predictions for which we searched in our data. Given the reproducibility of the location of the visual word and number form areas, we wondered whether these regions were already more connected with the temporo-frontal language network and the inferior parietal "number sense" regions than other mesial regions, which would explain their propensity to acquire the role of processing arbitrary shapes to represent phonemes or numbers. Similarly, we wondered whether hemispheric biases in connectivity at birth already predated the later lateralized responses to faces and words in the right and left fusiform gyrus (Weiner et al, 2016). We thus analyzed whether key regions of the linguistic network (i.e. pars triangularis of the inferior frontal gyrus, superior and middle temporal gyrus) are differently related to the left and right ventral temporal regions.

Methods

1. Subjects

Twenty-four healthy full-term neonates scanned for research purposes were included in this study. The fMRI data were provided by the Karolinska University Hospital, Stockholm (14 neonates) and by the Centre for the Developing Brain, King's College London (10 neonates) and have already been published (Fransson et al, 2009; Doria et al, 2010). All MR examinations were

carried out according to the ethical guidelines and declarations of the Declaration of Helsinki (1975). Details can be found in the seminal papers. Six subjects were subsequently rejected due to excessive movement artefacts (see preprocessing section). We thus analyzed 16 girls and 9 boys aged 41.1 weeks (std: 1.08) in average at scan.

2. MR Image Acquisition

For the Swedish cohort, infants were scanned during natural sleep. Functional MRI scans were acquired on a Philips Intera 1.5 Tesla scanner equipped with a 6-channel receive-only head coil. Echo planar imaging (time repetition [TR]/time echo [TE]/flip angle = 2000 ms/50ms/80º, voxel size=2.8 x 2.8 x 4.5 mm, 20 slices) of the infant brain was performed for 10 minutes (300 EPI volumes). For the London cohort, infants were sedated with chloral hydrate (25–50 mg/kg) and images were acquired at 3 Tesla (Achieva, Philips, Best, Netherlands) with an 8 channel phased array head coil. Echo planar imaging (TR/TE/flip angle = 1500ms/45ms/90º, 2.5 x 2.5 x 3.25mm, 22 slices) was performed for 6.4 minutes. In both groups, T1-weigthed images were acquired in each neonate. Although it is unconventional to merge data obtained from two different MRI scanners for combined group-level inference, we were confronted to the scarcity of the publically available data at this age and the small size of the groups. Note that our first-level comparisons were computed within-subject searching for differences in functional connectivity between voxels. By merging the two groups, we probably increased the variance between subjects but we benefited from more degrees of freedom. To capture the group differences, a group-factor was declared in our statistical analyses.

3. Preprocessing.

FMRI images were all pre-processed using SPM8 (Wellcome Institute of Imaging Neuroscience, London, UK) implemented in Matlab (Mathworks, Natick, MA). Pre-processing

involved within-subject realignment to account for head motion, spatial normalization to a template and smoothing: all images were realigned to the mean image of the resting state session using linear transformations. The mean EPI image was spatially normalized to a 7 week-old infant template image for whom a sulci-based parcellation is available (Kabdebon et al., 2014), thus providing anatomically defined region of interests to study functional connectivity. Brain growth and sulcation massively develop during the last trimester of gestation but decelerate after term-age. Although tertiary sulcation begins around full-term birth and continues to develop until adulthood, all main structures important for normalization are visible (see Kabdebon et al, 2014, for quantitative measures of inter-age variability of the location of the main sulci during the first semester of life). The transformation parameters obtained from this spatial normalization were subsequently applied to every functional image acquired during the resting state scanning session with a target voxel size of 2x2x2 mm^3. Then, spatially normalized images were smoothed with an isotropic 5-mm^3 full-width half-maximum Gaussian kernel. Next, we regressed out the effect of the following nuisance variables from the voxel time series using the REST toolbox for Matlab (http://restfmri.net): the six movement parameters from the head motion correction stage along with the global signal of the entire brain and four nuisance signals obtained from a 3-mm sphere located in the ventricles and white matter. Finally, all functional MRI time series were band-pass filtered (0.01 - 0.08 Hz).

Spontaneous movement during sleep in infants often consists of sudden hyperextensions along the body axis which produced spiking artefacts in the time series and might have therefore disrupted anterior-posterior correlations as a result of these pitch movements. Because subject motion is particularly deleterious on long-distance correlations (Power, Schlaggar, & Petersen, 2015), we removed the artifacted time points through a semi-automatic method. First, we deleted

brain volumes detected by the ART toolbox for SPM8 as contaminated by high levels of movement. Second, we visually inspected whether all traces of movement were removed from the voxel time series. When needed, more brain volumes were discarded until no trace of movement was visually detected in the time series. Concerns about such scrubbing have been raised in the literature as it decreases the degrees of freedom and destroys the temporal time-series when too many successive brain volumes are removed (for a discussion see Power et al., 2015). Furthermore, given the non-stationarity of the functional correlations, some stages during which subjects might naturally move may be under-represented. These concerns are particularly critical when different populations with different levels of agitation are compared, such as infants with adults. However, this concern does not apply to our study, since we are comparing the connectivity between different voxels that have been similarly processed within subjects. In the end, six subjects whose remaining time-series were shorter than 130 scans were discarded to avoid noisy correlation estimations. All included subjects had at least 138 brain volumes (mean number of volumes: 218, SD: 47, min: 132, max: 300). We also estimated the temporal signal to noise ratio (tSNR) for every voxel of every infant, as the inverse of the coefficient of variation in time (tSNR = mean /stdev of the times series). There was no difference between the two groups ($t(22)= 1.25$, $p= 0.22$).

4. Clustering analysis

To parcel the ventral areas in clusters of voxels with similar patterns of functional correlation, we applied the following data-driven clustering method. First, we performed a functional correlation analysis (Brain Voyager, Neuroelf v1.0, http://neuroelf.net/) seeded from each voxel belonging to a mask of the ventral stream of the visual cortex, i.e., ventrally to the Calcarine sulcus expanding towards the anterior parahippocampal gyrus and limited to y= -14 in the template (1484 voxels, corresponding to the union of the clusters presented in figure 1). In

other words, in each individual neonate, time-series were extracted from each functional voxel within the mask z-normalized and used as general linear model (GLM) predictors. For each voxel in the mask, random-effects inference was then performed on the group level. Second, each resulting group-level map was masked by a gray-matter mask, thresholded (voxelwise $p<0.01$ uncorrected), binarized and reshaped into a numerical vector. We then represented the functional correlation from all seeds as a matrix of 1 484 columns (the number of seeds) and 14 808 rows (the number of gray-matter brain voxels). Third, we used an agglomerative hierarchical clustering algorithm to cluster the seed voxels with a similar spatial pattern of functional correlation (i.e. a similar matrix columns). A hierarchical cluster tree was constructed using the Ward linkage measure on Euclidean distances (minimum variance algorithm merging at each step the pair of clusters that leads to the minimal increase in total within-cluster variance). The final number of clusters was optimized using the silhouette technique which quantifies the ratio between the largest inter-cluster distance over the smallest distance to a point outside the cluster. An assessment of all solutions in the range of 2 to 15 clusters showed a local maximum for 4 clusters. Fourth, in order to study the brain networks correlated with each of these 4 clusters, we performed a group-level analysis similar to the one described above, but using the average time-series from all the voxels of each cluster computed in each individual neonate. We also computed partial correlation coefficients for each cluster in order to regress out the time-series of all other clusters and thus obtain its unique correlation pattern (figure 1). Significance thresholds were set to $q=0.01$ (FDR-corrected for multiple comparisons) when using partial correlation and $q=0.001$ (FDR-corrected for multiple comparisons) when using Pearson's correlation.

5. Seed analysis

Clustering analyses provide a coarse grouping of voxels with similar connectivity tendencies but blind to anatomical boundaries. To reveal a finer dissection of the ventral connectivity, we used the anatomical parcellation proposed by Kabdebon et al (2014) on a two-month-old infant template to define defined four ROIs, based on the gray matter of 4 sulci bordering the lingual, fusiform (internal part), fusiform (external part), and the inferior temporal gyrus.. Those ROIs were used as seeds for the correlation analysis (figure 2a). For each subject and each ROI, we defined the time-series *T* as the average time-series across all the voxels within the ROI. Then, we calculated the Pearson correlation between *T* and the time-series of all the voxels in the brain, *V*. Through this procedure, we obtained 4 correlation brain volumes or maps per subject *s* and ROI *r* ($C_{s,r}$), which were Fisher-transformed (Matlab function atanh) to produce $Z_{s,r}$. To test for significant correlations across subjects between *T* and all voxels in the brain, we performed a one-way t-test on each ROI r, setting the significance value at $p < 0.01$, FDR-corrected voxelwise. We also performed a within-subjects ANOVA between maps so as to compare pairs of $Z_{s,r}$ for each individual subject, setting the significance value at $p < 0.01$ for visualization purposes (a more strict threshold of $p < 0.001$ did not qualitatively change the results).

6. Regression analysis

Given that the boundaries between ROIs in the previous analysis were based on sulci that might not follow cytoarchitectonic boundaries (Fischl et al., 2008), we also performed an analysis free of this constraint through voxel-wise regression to explore the mesial-to-lateral gradient in a ROI-independent manner. We constructed a mask comprising both left and right ventral regions (Figure 4a). We reduced this mask to a x,y grid along the left-right and antero-posterior axes, merging together all voxels along the *z* axis (dorsal-ventral axis), as the mosaic of activations to visual categories that we wanted to explore is mainly evident along these two axes (Weiner et al,

2016). We computed the correlation map for each x,y pair and the time series of all voxels in the brain in each subject and obtained a total of 276 (for left hemisphere) and 258 (for right hemisphere) correlation maps per subject. to identify regions whose correlation with voxels in the ROI would depend on their x and y coordinates, we performed a first-level regression analysis (using SPM) for each subject. We then submitted the x-related contrast to a second-level analysis, in order to quantify the influence of the x coordinate on functional correlation. We modeled the cohort origin (i.e. England or Sweden) explicitly as blocks in the analysis. The resulting second-level beta map and its associated t-map revealed the relation between the x-axis and functional correlation: the higher the beta and the t value, the more connected each voxel was with increasing values of x (i.e. from medial to lateral localization). Conversely, the smaller the effect the more connected each voxel was with decreasing values of x. We performed this procedure for the left and the right hemispheres, inverting the x values when necessary to keep the convention that increasing x values correspond with lateral locations.

We wondered whether the differences we observed between mesial and lateral regions were related to their level of maturation which might have created different delays in neurovascular coupling. As a control procedure aimed at accounting for this possibility, we repeated the analysis including the average T2 value of the template brain at the same locations as a regressor and thus a proxy for maturation index (Leroy et al., 2011).

7. Analysis of hemispheric differences

Because the VWFA and the FFA are respectively left and right lateralized in adults, we studied whether differences in functional correlation were observed early in development, between the ventral areas and key regions of the linguistic network. Therefore, we recovered the following anatomically pre-defined ROIs from the infant atlas provided by Kabdebon et al. (2014): the pars

triangularis of the inferior frontal gyrus (region number 4 in the atlas), the middle temporal gyrus (region 27) and the superior temporal gyrus (region 28). We truncated regions 27 and 28 along the anterior-posterior axis at the level of the deepest angle of the *planum temporale* so as to keep the ROIs most anterior parts. This was done to avoid any overlap or vicinity of the seeds with the visual stream that could have biased the analysis with spurious local correlations.

For every subject and every pair of left-right regions, (e.g. left and right pars triangularis), we performed two seed analyses, the first between the left ROI time-series and the rest of the brain and the second using the right ROI time-series. We thus obtained two functional correlation maps per subject and ROI pair. To test for hemispheric laterality biases, we performed a series of t-test (for each value of x coordinate) on the left-right difference collapsing all y-coordinate values between values of y coordinate of 9 and 13. The significance threshold was set at $p < 0.05$, Bonferroni corrected for multiple comparisons (42 comparisons, corresponding to the 42 voxels along the x coordinate).

Results

1. Parcellation of visual ventral regions

We first performed a data-driven clustering of the voxels in the bilateral ventral regions according to their functional correlation pattern. Voxels were clustered together or separately as a function of the similarity of the pattern of correlation with the entire brain. This clustering procedure was combined with a partial correlation analysis in order to display the unique functional fingerprint of each cluster (i.e. not shared with other clusters). We identified four main clusters: C1, or Medial Occipital, posterior, an exclusively posterior occipital group connected with the frontal pole, the right inferior temporal gyrus and paracentral regions consisting of the right post-central gyrus, paracentral lobule and supplementary motor area; C2, or Medial Occipital,

anterior, connected with neighboring mesial areas (lingual, fusiform, parahipocampal gyri, and the cuneus) and more distant primary regions, such as the central sulcus, Heschl's gyrus, *planum temporale*, bilateral posterior insula and the center of the right STAP region (the STAP is a region of the superior temporal sulcus under Heschl's gyrus, deeper in the right than in the left hemisphere in almost all humans, Leroy et al., 2015); C3, or Anterior Lateral, a cluster which had the most extended unique functional correlation, connected to the inferior and middle temporal lobes, the inferior parietal regions comprising the inter-parietal sulcus, and the precentral gyri; C4, or Posterior Lateral, a cluster connected to the dorsal visual steam, cuneus and left dorso-lateral prefrontal region (Figure 1 for functional correlation using Pearson's correlation).

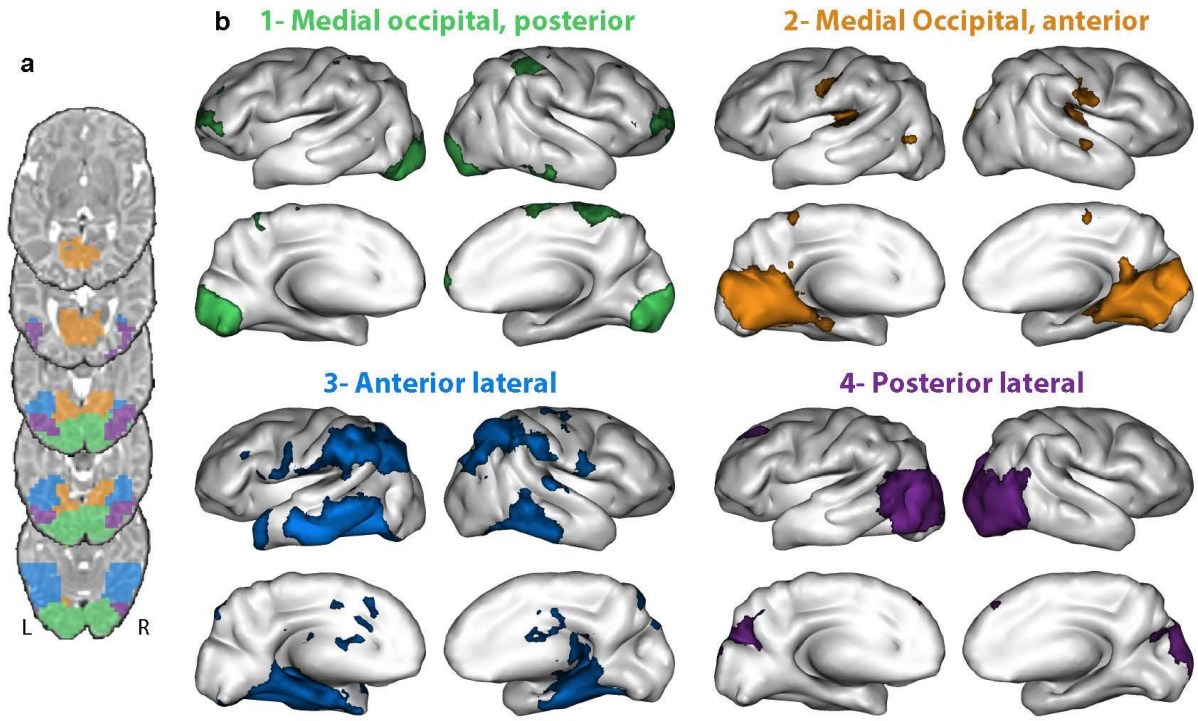


Figure 1. **Clustering of ventral visual cortex according to long-distance whole-brain functional correlations in newborns.** a) Four clusters were identified and are presented by

different colors on axial slices of the infant template. b) Partial correlation maps showing the distinct patterns of whole-brain correlations associated with each of the four clusters. All clusters exhibit long-distance functional correlations, but the most lateral and anterior cluster (C3) appears to be specifically correlated to inferior parietal and frontal associative areas.

2. Functional correlation based on anatomical ROIs

The parcels defined above correspond to an optimal statistical solution given our data but may differ from the anatomical reality. We thus sought to confirm the above conclusions using four anatomical ROIs progressively aligned along the medial-external axis of the left ventral temporal cortex in order to determine how they connected to the rest of the brain. As expected from the previous analysis, the observed functional correlation was not limited to neighboring ipsilateral areas or to homologous regions in the right hemisphere (figure 2). Rather, the connections crossed hemispheres to join distant associative areas in the right hemisphere. We observed a different correlation pattern depending on ROI position (Figure 3a, b): the most mesial ROI (ROI1, or Lingual gyrus) functionally related to the superior temporal region as well as central motor and sensory regions whereas the most lateral ROI (ROI4, inferior temporal gyrus) was principally correlated with the whole temporal lobe, the inferior parietal region and the prefrontal region. ROIs 1 and 4 thus shared similarities with the clusters C2 and C3 of the previous analysis.

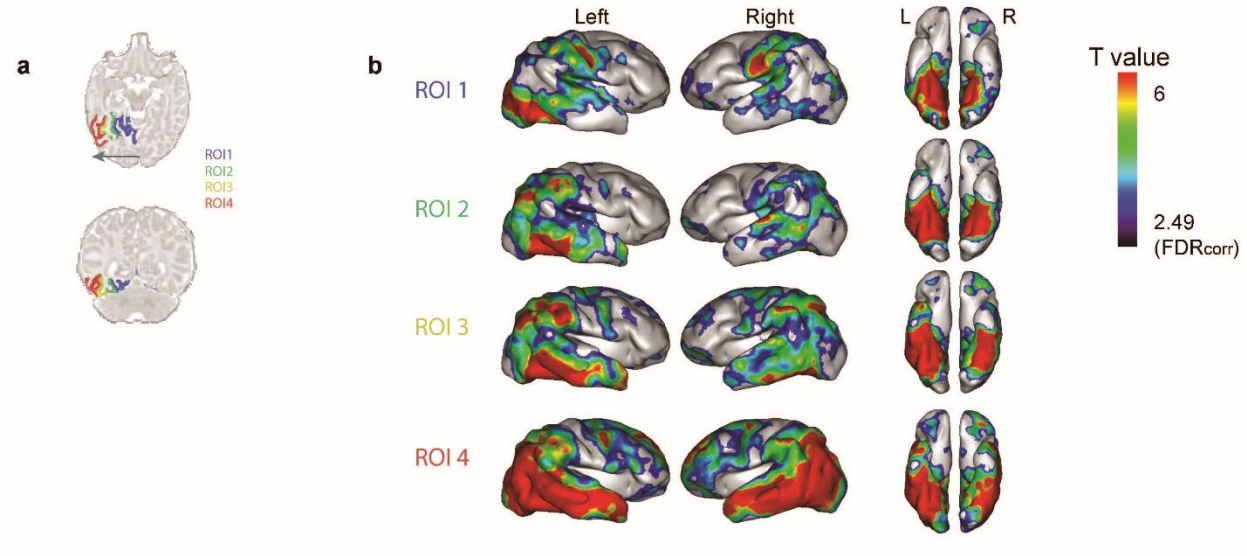


Figure 2. **A mesial-lateral gradient of functional correlation in ventral visual cortex.** a) The four ROIs used in this analysis as seeds, ordered from mesial to lateral. b) Functional correlations of the 4 ROIs, rendered on a 3D infant inflated brain. p = 0.01, FDR corrected.

Pairwise comparisons between the patterns of functional correlation of the different ROIs (figure 2) revealed that ROI1 (lingual gyrus) was most strongly correlated with the lower part of the central sulcus and Heschl's gyrus bilaterally. ROI2, the medial part of the fusiform gyrus presented only local correlations which extended more anteriorly in the left fusiform and inferior temporal gyri relative to ROI1. A sharp change occurred with ROI3, the lateral part of the fusiform gyrus, which displayed correlations with the ventral regions in both hemispheres and moreover with the supra-marginal and angular gyri, also in both hemispheres. This change corresponds to the mid-fusiform sulcus, separating the internal and external part of the fusiform gyrus (Weiner et al., 2014). Finally, ROI4 (inferior temporal gyrus) displayed the most extended correlation pattern, exhibiting stronger correlations with the whole temporal lobe and prefrontal regions relatively to the other ROIs and notably to ROI3. It is noticeable that the significant changes of functional

correlation patterns between the lateral part of the fusiform (ROI3) and the inferior temporal gyrus (ROI4) spared the parietal and frontal regions.

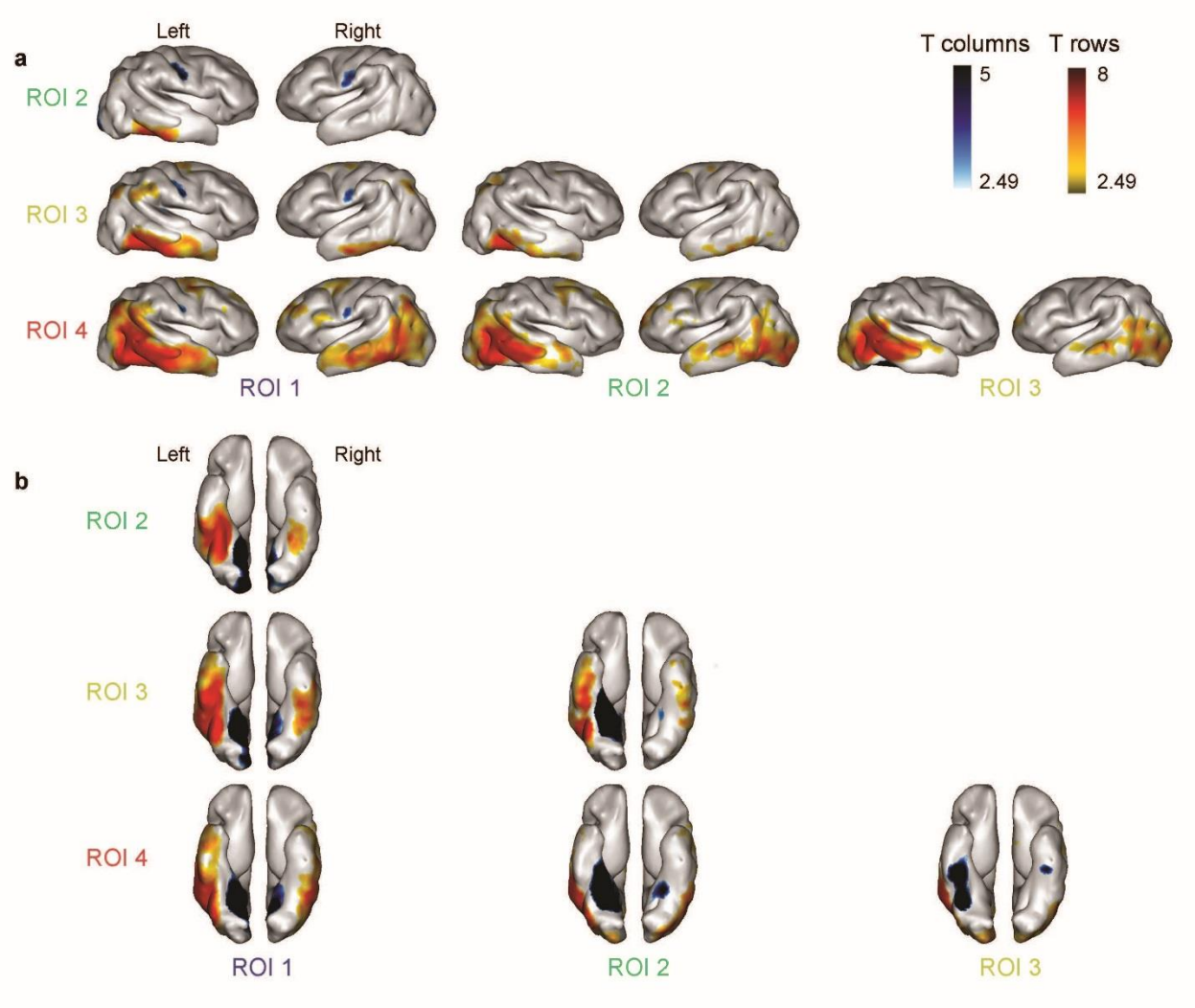


Figure 3. **A mesial-lateral gradient of functional correlation in ventral visual cortex.** ANOVAs. a) The connectivity patterns of each pair of ROIs are compared two by two. Each column presents the t-contrast row ROI > column ROI. (For illustration purposes, p-value was set at $p < 0.01$, uncorrected.) A mesial-to-lateral gradient is clearly visible: mesial seeds preferably correlate with primary regions, while lateral ROIs are more strongly related to associative regions in the temporal, parietal and frontal lobes.

A possible confound is a similar neurovascular coupling in regions at the same maturational stage. While there is no indication that equally maturating regions will show a correlated functional activity in time, to account for this possibility we repeated the analysis including the average T2 value of the template brain at the same location as a regressor and thus as a proxy for maturation index (Leroy et al., 2011). Because dendritic development impairs water motion in the gray matter and myelination in the white matter, T2 signal becomes progressively darker during the first year of life and can hence be used as a proxy for neural maturation (Leroy et al., 2011). We observed virtually the same functional correlation pattern, suggesting that maps presented in figure 2 are not directly related to a maturational neuro-vascular gradient.

A third, voxel-wise, analysis aimed to verify that the mesial-to-lateral organization of the fusiform gyrus was not biased by our arbitrary, although anatomical, ROI definition. To this aim, we examined the functional correlation between each x,y location in a ventral region encompassing the calcarine sulci, lingual gyrus, fusiform gyrus and inferior temporal gyrus and examined the dependency of this functional correlation pattern on the x-coordinate of the voxel of origin (see Methods). In agreement with our previous ROI analysis, functional correlation was sensitive to the x-coordinates (figure 4): Heschl's gyrus and posterior insula signal showed a greater functional correlation with mesial voxels in the ventral visual cortex (thus appearing as a negative correlation in figure 4b), whereas associative areas of the temporal lobe (sparing the superior temporal region) in both hemispheres, the left angular and supramarginal gyri and both prefrontal regions showed a greater functional correlation with lateral voxels (thus appearing as a positive correlation in figure 4b; see Table S2).

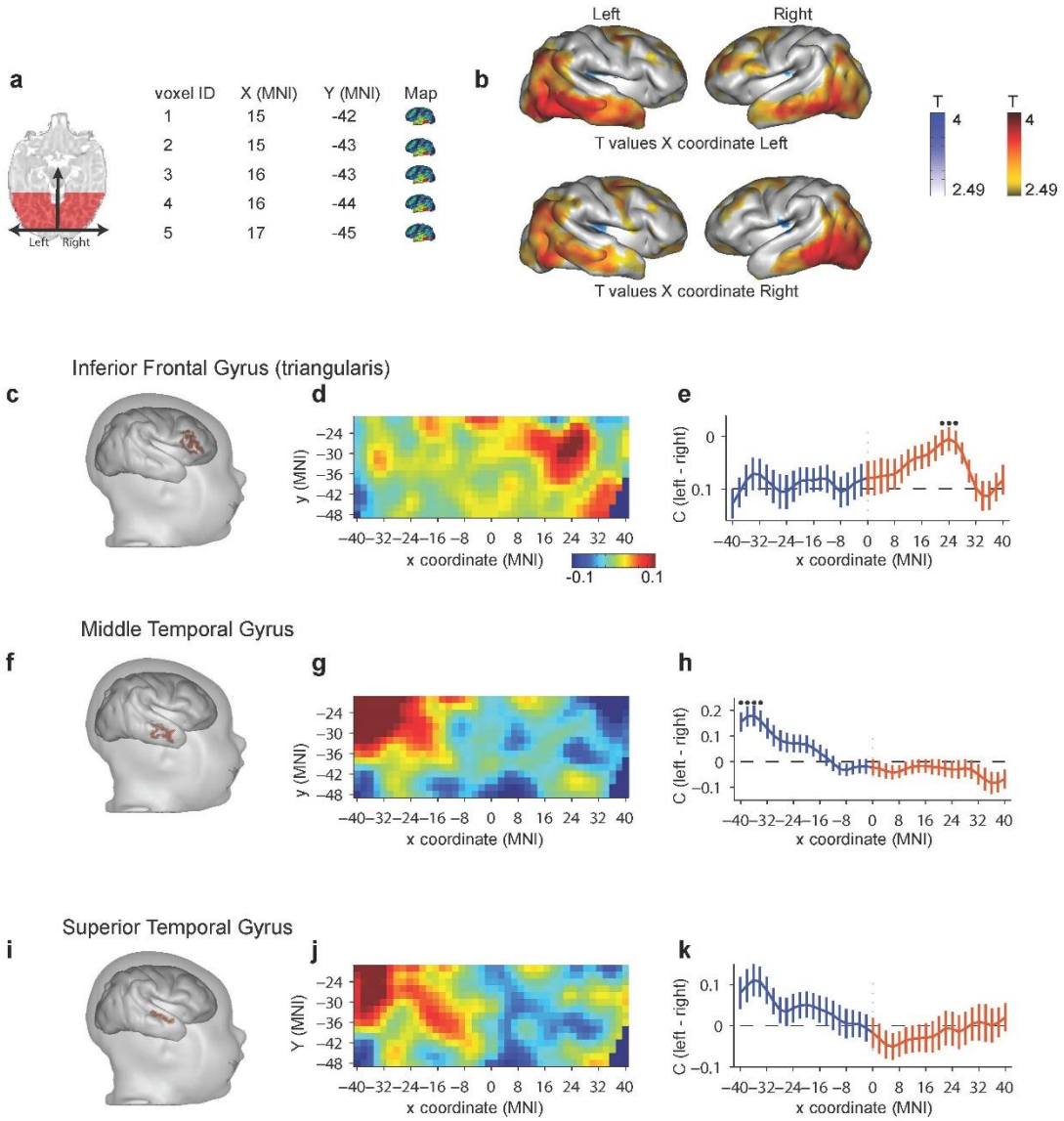


Figure 4. **Hemispheric differences in long-distance functional correlations.** a) The mask containing all voxels used as seeds in the regression analysis is presented on a horizontal slice. To quantify to what extent functional correlations vary with the x-coordinate, a connectivity map was computed for each voxel in this mask and was subsequently entered into a regression analysis with the x coordinate as a regressor. b) Functional correlation pattern as a function of the x-axis location of the seed in the left and right hemispheres. The more positive the value, the stronger the correlation with lateral voxels (e.g. the right inferior frontal region with a lateral left seed) whereas

the more negative the value the stronger the correlation with mesial voxels (e.g. Heschl's gyrus on both sides). c-k) Analyses of hemispheric biases. c, f, i display the location of the three bilateral ROIs used as seeds: inferior frontal gyrus (c), medial temporal gyrus (f) and superior temporal gyrus (i). d, g, j display the flat projection of the ventral areas, showing the difference in functional correlation between the left and right seeds (voxels more connected with the left seed appear in red, whereas those more connected with the right seed appear in blue). The grid corresponds to the mask presented in (a). e, h, k) The differences between left and right functional correlation values are plotted as a function of the x coordinate. Dots over the curve mark the spots where the difference in connectivity is significantly different ($p < 0.05$, Bonferroni corrected).

3. Hemispheric asymmetries

Finally, to study putative asymmetries in the manner in which right and left ventral streams relate to the language network, we performed a within-subject comparison of the functional correlation maps arising from three pairs of symmetrical anatomical ROIs located at key language-related areas: pars triangularis in the inferior frontal gyrus (IFG), superior and middle temporal gyri (STG and MTG). Figures 4c-4k thus show to what extent each site in the left and right ventral visual cortex was more strongly correlated to the left or right IFG, STG and MTG. Unsurprisingly, STG and MTG exhibited a stronger correlation with the ipsilateral than with the contralateral hemisphere, but this relation was stronger in the left hemisphere at a peak close to the location of the VWFA in adults (x=-36 and y =-30, MNI coordinates). After correction for multiple comparisons, this peak remained significant only for the MTG (Figure 4 g, j). More surprisingly, the left IFG signal was more correlated than the right IFG with a right lateral ventral spot at x=24 and y =-30 (MNI coordinates).

Discussion

We explored the pattern of functional correlations of the ventral visual cortex with the rest of the brain in sleeping full-term neonates. Both of our analyses, whether data-driven (figure 1) or based on anatomically defined regions (figure 2), revealed a clear partition of the ventral regions supporting the hypothesis of an early functional organization. Mesial ventral areas were notably correlated with other primary regions whereas the most lateral regions were more correlated with the whole temporal lobe, the inferior parietal region and the prefrontal region with a transition occurring between ROI 2 and 3 (figure 2). This boundary roughly corresponds to the mid-fusiform sulcus which splits the fusiform gyrus (Weiner et al, 2014). This sulcus has been proposed as a robust cyto-architectonic landmark between FG1 and FG3 on one side and FG2 and FG4 on the other side, and functional landmark between the place area and the FFA/VWFA in adults (Weiner et al., 2014; Weiner et al., 2016). Finally, studying hemispheric differences in functional correlations, two results emerged: (1) when comparing intra-hemispheric correlations, we observed a stronger correlation between the middle temporal gyrus and the fusiform region in the left than in the right hemisphere, and (2) for interhemispheric correlations, we observed a stronger correlation between a right lateral ventral area and the contralateral left IFG than with the ipsilateral right IFG.

This organization of the associative visual regions is all the more remarkable given that vision is very limited *in utero*, contrary to the other senses which are regularly stimulated through the fetus' spontaneous movements, internal and external sounds crossing the maternal abdomen, and a tasty and odorant amniotic liquid reflecting the mother's meals. This early organization of the visual areas at birth, beyond primary areas, dismisses the old but persisting idea of a blank slate newborn (Johnson, 2011; Elman et al., 1996). Although the human infant appears immature at birth due to his poor motor repertoire, early learning is thus supported by a pre-existing cortical

architecture now extensively documented by a decade of functional brain imaging studies in infants (Bartocci, Bergqvist, Lagercrantz, & Anand, 2006; Arichi et al., 2010; Mahmoudzadeh et al., 2013; Mahmoudzadeh, Wallois, Kongolo, Goudjil, & Dehaene-Lambertz, 2016; Sours et al., 2017; Toulmin et al., 2015).

Our working hypothesis went beyond a mere organization at birth, and we studied whether the functional specificity described at later ages in ventral temporal areas for visual categories such as words, faces, tools and places might partly be based on a pre-existing pattern of functional correlation of these regions with the rest of the brain ("biased connectivity" hypothesis) contrasting with the hypothesis of an initially diffuse connectivity only secondarily refined through exposure to a given environment (Johnson, 2011; Elman et al., 1996). Anatomically, long-range pathways, in particular those connecting frontal regions with temporal and occipital regions can be observed in post-mortem brains from the second trimester of gestation on (Takahashi, Folkerth, Galaburda, & Grant, 2011). Even if the tracts are initially not well myelinated, the structural architecture of the human brain set up during the last month of gestation offers the possibility of long-distance synchrony. Previous studies of functional correlations in full-term and preterm neonates have indeed reported a set of maps of functionally synchronized regions similar to those observed in adults (Fransson et al., 2007, 2009, 2011; Doria et al., 2010; Smyser et al., 2010, 2011) Here, we explored whether a finer-grained pattern of functional correlation was present within ventral visual cortex, correlating with the functional specificity for visual categories observed in adults.

Our results indicate that the most lateral regions are more connected to distal associative regions, notably in the frontal lobe, than mesial regions are (compare cluster 3 and ROI 4 (inferior temporal gyrus) to cluster 2 and ROI 1 (lingual gyrus) in figures 1 and 2, respectively). The privileged connectivity of such lateral regions residing at the top of the hierarchy of early visual

regions may thus explain why the cultural symbols of letters and digits later develop at this location. This aspect of our results corroborate prior findings in older children, which have indicated that anatomical connectivity prior to reading acquisition (at 5 years of age) of ventral visual voxels to temporal and frontal regions was predictive of those voxels which would later exhibit a preference for written words at 8 years of age, once children had learned to read (Saygin et al., 2016). In both cases, connectivity (anatomical or functional) precedes functionality, thus supporting the "biased connectivity" hypothesis for the origins of ventral visual specialization.

By contrast, we found that mesial areas are functionally more connected to sensorimotor areas, Heschl's gyrus and the posterior insula. This observation could be mediated by direct connections between visual primary areas and auditory and parietal cortices which have been reported in newborn kittens (Innocenti, Berbel, & Clarke, 1988) and adult macaques (Rockland & Ojima, 2003). Alternatively, the observed functional correlation between mesial visual regions and other primary cortices (auditory areas and motor sensory areas at the level of the mouth and tongue) could also be driven by thalamic synchrony. Alcauter et al (2014), studying thalamo-cortical connectivity during infancy, reported an overlap of the connectivity between primary visual, auditory and sensory-cortices within the same thalamus cluster in neonates, whereas distinct clusters were observed at one year of age. Contrarily, Toulmin et al (2015) described a more segregated thalamo-cortical connectivity from birth on, especially concerning the primary cortices. We may speculate that an initial stage of multisensory integration might facilitate learning by enhancing responses to co-occurring cues that need to be integrated into higher-level representations. For example, it might explain the observations that neonates visually recognize their mother only if they have been simultaneously exposed to her face and voice (Sai, 2005) and

that 3-month-olds more robustly identify their mother vs. a stranger's face if her voice is simultaneously presented (Burnham, 1993).

This mesial-lateral division of functional correlation was similarly observed in the left and right hemisphere (see figure 4b) and may correspond to the cyto-architectonic division highlighted in adults by Weiner et al. (2014, 2016), and to the functional parcellation of activations revealed in older infants looking to faces/objects vs. places images (Deen et al., 2017). In both hemispheres, long-distance functional correlation was not limited to within-hemispheric areas, but also recruited contra-lateral heterotopic areas encompassing the inferior parietal and dorsal frontal regions. Although roughly similar, interesting differences were observed between the two hemispheres. Because the VWFA is systematically lateralized to the hemisphere involved in spoken language processing (Pinel & Dehaene, 2009; Pinel et al., 2014; Cai, Paulignan, Brysbaert, Ibarrola, & Nazir, 2010), which is usually in the left hemisphere, we examined the functional correlation at birth between three key regions of the spoken language network and ventral visual areas (figure 4c-i). The STG and MTG were strongly connected with both the ipsi- and contra-lateral visual regions, but the left MTG was significantly more related with the left lateral extra-striate visual region than its right counterpart. Thus, a stronger path already exists at birth between the spoken language network and the future location of the VWFA. It may explain why reading acquisition always recruits this particular location within the left ventral visual cortex (Hannagan, Amedi, Cohen, Dehaene-Lambertz, & Dehaene, 2015).

The significant trans-hemispheric correlation between the left inferior frontal region and the right lateral ventral visual cortex was more surprising. This cluster is more mesial than the cluster discussed above (~24 vs -38 mm in our mask x-coordinates). Contrary to temporal regions, left and right inferior frontal regions were weakly correlated with ventral voxels in our mask except

for this particular relation between this right cluster and the left frontal region. Note that in figure 4b, in which we studied the functional correlation of the left and right ventral temporal regions, we also observed a crossed relation yet in the reverse direction between the left temporal region and the right inferior frontal region. Does this functional correlation pattern correspond to a genuine, anatomically validated pathway? In rare patients with a developmental agenesis of the corpus callosum, sigmoid bundles connecting the right frontal region with the left contra-lateral occipital region (and, even more rarely, the converse pattern) have been detected by diffusion-tensor imaging (Benezit et al., 2015; Tovar-Moll et al., 2007). On one hand, these cases may correspond to aberrant bundles. On the other hand, the absence of a corpus callosum may reveal a smaller tract, otherwise masked by the large corpus callosum. Indeed, in a post-mortem tracing study in a single adult human brain, Virgilio and Clarke (1997) were able to identify the degenerating axons in a patient who died a few weeks after a stroke in the right inferior temporal region and reported inter-hemispheric mono-synaptic connections between the right inferior temporal region and the left-hemispheric Wernicke's and Broca's areas. Thus, interhemispheric connections can be heterotopic and relate widely different regions, in agreement with the present results. Our functional correlation pattern may also be related to a rare study of face processing in infancy by Tzourio-Mazoyer and collaborators (2002). Using positron emission tomography, these authors reported activations in left inferior frontal and left superior temporal cortex, together with right fusiform cortex, when two-month olds were looking at faces. Efficient connections between right-hemispheric fusiform face representations and left-hemispheric language areas might explain why vocal imitations can be so easily elicited when infants view articulating faces (Bristow et al., 2009; Chen, Striano, & Rakoczy, 2004; Meltzoff & Moore, 1977). Future studies in larger groups

should reveal whether these observations are anecdotal or reflect robust structural connections present in most of the neonates.

Although we studied a relatively small number of infants here, we observe a clear parcellation of the visual areas, that speak to major theories on the origins of functional specialization in the adult human brain. The present resultsshow that the neonate connectivity landscape is very far from a "blooming buzzing confusion" (James, 1890). As such, the refute theories of an extreme empiricist nature, which assumes that the infant brain is largely devoid of initial architecture and that connectivity is initially diffuse, over-abundant and largely isotropic, and only becomes refined at a later stage during infancy and childhood through exposure to a given environment (Johnson, 2011; Elman et al., 1996; Quartz & Sejnowski, 1997). Ventral visual cortex is not just "trained" by exposure to objects, faces, houses, letters or digits; on the contrary, it contains functionally specialized areas already present at the dawn of infancy (Deen et al., 2017; Biagi, Crespi, Tosetti, & Morrone, 2015), supported by well-defined fiber tracts. Several previous studies have already shown how at a global scale, an organized functional and anatomical connectivity is present in the infant brain (Fransson et al., 2007, 2009, 2011; Doria et al., 2010; Smyser et al., 2010, 2011; van den Heuvel et al., 2015). Here we show a refined organization within a single region with a gradient of preferred relations with local and distant regions, in accordance with the hypothesis of an early organization ("protomaps") determined during gestation (Rakic, 1988; Mahmoudzadeh et al., 2016; Toulmin et al., 2015). These maps provide neonates with a blueprint on which learning capitalizes.

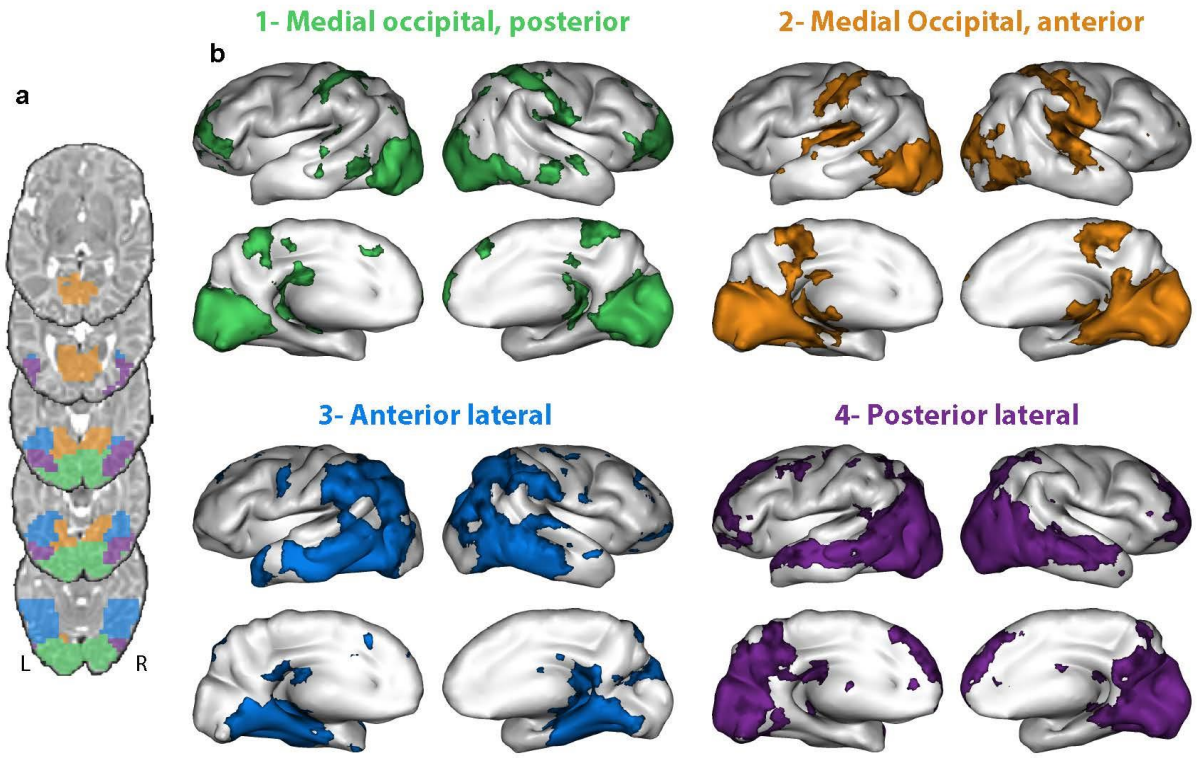
While indisputable differences in functional correlation were found between mesial and lateral regions, we did not recover a full adult-like organization. For instance, given the systematic location of word- and number-form areas in adults (VWFA and NFA), with the NFA

systematically occupying a location lateral to the VWFA (Shum et al., 2013; Amalric & Dehaene, 2016; Hannagan et al., 2015), we could have expected a differential pattern of connectivity, with the most lateral ventral visual voxels projecting preferentially to the inferior parietal lobe which has been implicated in number sense; however, such was not the case. That being said, our group was small merging two different groups of infants and our method was crude in the sense that we did not know precisely which cortical sectors, in our infants, would later become specialized for letters versus digits, unlike what had been done in older children (Saygin et al., 2016). Future studies with an improved methodology might reveal that the infant brain contains even finer-grained biases that predate the fine differences between VWFA and NFA seen in adults. Alternatively, it is possible that such patterns of functional specialization emerge through exposure and learning and that initially only a rough division between mesial and lateral regions is visible. In line with this idea, Deen et al (2017) reported clear differences between fMRI activations for faces vs. places but not for objects vs. faces in 4-6 month-old infants. Similarly, Gomez et al. (2017) underlined the protracted development of the fusiform region sensitive to face relative to more mesial areas. The acquisition of longitudinal data in the same children from infancy to childhood, although extremely difficult, may be necessary to answer this question.

Acknowledgements

Authors would like to thank Elvis Dohmatob, Isabelle Denghien, François Leroy, Jessica Dubois for their constructive remarks during this work.

Supplementary material



Supplementary Figure 1. **Clustering analyses using Pearson correlation** a) The 4 clusters identified in this analysis are presented on a horizontal slice of the infant template. b) Pearson correlation maps showing whole brain connectivity specifically related to each of the 3 defined clusters.

REFERENCES

Amalric, M., & Dehaene, S. (2016). Origins of the brain networks for advanced mathematics in expert mathematicians. *Proc Natl Acad Sci U S A, 113*(18), 4909-4917. doi:10.1073/pnas.1603205113

Arichi, T., Moraux, A., Melendez, A., Doria, V., Groppo, M., Merchant, N., . . . Edwards, A. D. (2010). Somatosensory cortical activation identified by functional MRI in preterm and term infants. *Neuroimage, 49*(3), 2063-2071. doi:S1053-8119(09)01109-4

10.1016/j.neuroimage.2009.10.038

Bartocci, M., Bergqvist, L. L., Lagercrantz, H., & Anand, K. J. (2006). Pain activates cortical areas in the preterm newborn brain. *Pain, 122*(1-2), 109-117.

Biagi, L., Crespi, S. A., Tosetti, M., & Morrone, M. C. (2015). BOLD Response Selective to Flow-Motion in Very Young Infants. *PLoS Biol, 13*(9), e1002260. doi:10.1371/journal.pbio.1002260

Cai, Q., Paulignan, Y., Brysbaert, M., Ibarrola, D., & Nazir, T. A. (2010). The left ventral occipito-temporal response to words depends on language lateralization but not on visual familiarity. *Cereb Cortex, 20*(5), 1153-1163. doi:bhp175

10.1093/cercor/bhp175

Caspers, J., Palomero-Gallagher, N., Caspers, S., Schleicher, A., Amunts, K., & Zilles, K. (2015). Receptor architecture of visual areas in the face and word-form recognition region of the posterior fusiform gyrus. *Brain Struct Funct, 220*(1), 205-219. doi:10.1007/s00429-013-0646-z

Deen, B., Richardson, H., Dilks, D. D., Takahashi, A., Keil, B., Wald, L. L., . . . Saxe, R. (2017). Organization of high-level visual cortex in human infants. *Nat Commun, 8*, 13995. doi:10.1038/ncomms13995

Doria, V., Beckmann, C. F., Arichi, T., Merchant, N., Groppo, M., Turkheimer, F. E., . . . Edwards, A. D. (2010). Emergence of resting state networks in the preterm human brain. *Proc Natl Acad Sci U S A, 107*(46), 20015-20020. doi:1007921107

10.1073/pnas.1007921107

Dubois, J., Dehaene-Lambertz, G., Kulikova, S., Poupon, C., Huppi, P. S., & Hertz-Pannier, L. (2014). The early development of brain white matter: a review of imaging studies in fetuses, newborns and infants. *Neuroscience, 276*, 48-71. doi:10.1016/j.neuroscience.2013.12.044

Dubois, J., Poupon, C., Thirion, B., Simonnet, H., Kulikova, S., Leroy, F., . . . Dehaene-Lambertz, G. (2016). Exploring the Early Organization and Maturation of Linguistic Pathways in the Human Infant Brain. *Cereb Cortex, 26*(5), 2283-2298. doi:10.1093/cercor/bhv082

Elman, J. L., Bates, E., Johnson, M. H., Karmiloff-Smith, A., Parisi, D., & Plunkett, K. (1996). *Rethinking innateness: A connectionist perspective on development.* Cambridge, Mass.: MIT Press.

Fischl, B., Rajendran, N., Busa, E., Augustinack, J., Hinds, O., Yeo, B. T., . . . Zilles, K. (2008). Cortical folding patterns and predicting cytoarchitecture. *Cereb Cortex, 18*(8), 1973-1980. doi:10.1093/cercor/bhm225

Fransson, P., Aden, U., Blennow, M., & Lagercrantz, H. (2011). The functional architecture of the infant brain as revealed by resting-state fMRI. *Cereb Cortex, 21*(1), 145-154. doi:bhq071

10.1093/cercor/bhq071

Fransson, P., Skiold, B., Engstrom, M., Hallberg, B., Mosskin, M., Aden, U., . . . Blennow, M. (2009). Spontaneous brain activity in the newborn brain during natural sleep--an fMRI study in infants born at full term. *Pediatr Res, 66*(3), 301-305. doi:10.1203/PDR.0b013e3181b1bd84

Fransson, P., Skiold, B., Horsch, S., Nordell, A., Blennow, M., Lagercrantz, H., & Aden, U. (2007). Resting-state networks in the infant brain. *Proc Natl Acad Sci U S A, 104*(39), 15531-15536.

Glasser, M. F., Coalson, T. S., Robinson, E. C., Hacker, C. D., Harwell, J., Yacoub, E., . . . Van Essen, D. C. (2016). A multi-modal parcellation of human cerebral cortex. *Nature, 536*(7615), 171-178. doi:10.1038/nature18933

Gomez, J., Barnett, M. A., Natu, V., Mezer, A., Palomero-Gallagher, N., Weiner, K. S., . . . Grill-Spector, K. (2017). Microstructural proliferation in human cortex is coupled with the development of face processing. *Science, 355*(6320), 68-71. doi:10.1126/science.aag0311

Hannagan, T., Amedi, A., Cohen, L., Dehaene-Lambertz, G., & Dehaene, S. (2015). Origins of the specialization for letters and numbers in ventral occipitotemporal cortex. *Trends Cogn Sci, 19*(7), 374-382. doi:10.1016/j.tics.2015.05.006

Johnson, M. H. (2011). Interactive specialization: a domain-general framework for human functional brain development? *Dev Cogn Neurosci, 1*(1), 7-21. doi:10.1016/j.dcn.2010.07.003

Kabdebon, C., Leroy, F., Simmonet, H., Perrot, M., Dubois, J., & Dehaene-Lambertz, G. (2014). Anatomical correlations of the international 10-20 sensor placement system in infants. *Neuroimage, 99*, 342-356. doi:10.1016/j.neuroimage.2014.05.046

Kennedy, H., Douglas, R., Knoblauch, K., Dehay, C. (2007). Self-organization and pattern formation in primate cortical networks. *Novartis Foundation Symposium, 288*(178-194).

Kostovic, I., Judas, M. . (2010). The development of the subplate and thalamocortical connections in the human foetal brain. *Acta Paediatrica, 99*(8), 1119-1127.

Mahmoudzadeh, M., Dehaene-Lambertz, G., Fournier, M., Kongolo, G., Goudjil, S., Dubois, J., . . . Wallois, F. (2013). Syllabic discrimination in premature human infants prior to complete formation of cortical layers. *Proc Natl Acad Sci U S A, 110*(12), 4846-4851. doi: 10.1073/pnas.1212220110

Mahmoudzadeh, M., Wallois, F., Kongolo, G., Goudjil, S., & Dehaene-Lambertz, G. (2016). Functional maps at the onset of auditory inputs in very early preterm human neonates. *Cerebral Cortex*.

Marín-Padilla, M. (2011). *The Human Brain: Prenatal Development and Structure*: Springer-Verlag.

Pinel, P., & Dehaene, S. (2009). Beyond hemispheric dominance: brain regions underlying the joint lateralization of language and arithmetic to the left hemisphere. *Journal of Cognitive Neuroscience, 22*(1), 48-66.

Pinel, P., Lalanne, C., Bourgeron, T., Fauchereau, F., Poupon, C., Artiges, E., . . . Dehaene, S. (2014). Genetic and Environmental Influences on the Visual Word Form and Fusiform Face Areas. *Cereb Cortex*. doi:10.1093/cercor/bhu048

Power, J. D., Schlaggar, B. L., & Petersen, S. E. (2015). Recent progress and outstanding issues in motion correction in resting state fMRI. *Neuroimage, 105*, 536-551. doi:10.1016/j.neuroimage.2014.10.044

Quartz, S. R., & Sejnowski, T. J. (1997). The neural basis of cognitive development: a constructivist manifesto. *Behav Brain Sci, 20*(4), 537-556; discussion 556-596.

Raichle, M. E. (2015). The restless brain: how intrinsic activity organizes brain function. *Philos Trans R Soc Lond B Biol Sci, 370*(1668). doi:10.1098/rstb.2014.0172

Rakic, P. (1988). Specification of cerebral cortical areas. *Science, 241*(4862), 170-176.

Saygin, Z. M., Osher, D. E., Koldewyn, K., Reynolds, G., Gabrieli, J. D., & Saxe, R. R. (2012). Anatomical connectivity patterns predict face selectivity in the fusiform gyrus. *Nat Neurosci, 15*(2), 321-327. doi:nn.3001

10.1038/nn.3001

Saygin, Z. M., Osher, D. E., Norton, E. S., Youssoufian, D. A., Beach, S. D., Feather, J., . . . Kanwisher, N. (2016). Connectivity precedes function in the development of the visual word form area. *Nat Neurosci, 19*(9), 1250-1255. doi:10.1038/nn.4354

Shum, J., Hermes, D., Foster, B. L., Dastjerdi, M., Rangarajan, V., Winawer, J., . . . Parvizi, J. (2013). A brain area for visual numerals. *J Neurosci, 33*(16), 6709-6715. doi:10.1523/JNEUROSCI.4558-12.2013

Smith, S. M., Vidaurre, D., Beckmann, C. F., Glasser, M. F., Jenkinson, M., Miller, K. L., . . . Van Essen, D. C. (2013). Functional connectomics from resting-state fMRI. *Trends Cogn Sci, 17*(12), 666-682. doi:10.1016/j.tics.2013.09.016

Smyser, C. D., Inder, T. E., Shimony, J. S., Hill, J. E., Degnan, A. J., Snyder, A. Z., & Neil, J. J. (2010). Longitudinal analysis of neural network development in preterm infants. *Cereb Cortex, 20*(12), 2852-2862. doi:bhq035

10.1093/cercor/bhq035

Smyser, C. D., Snyder, A. Z., & Neil, J. J. (2011). Functional connectivity MRI in infants: Exploration of the functional organization of the developing brain. *Neuroimage*. doi:S1053-8119(11)00250-3

10.1016/j.neuroimage.2011.02.073

Sours, C., Raghavan, P., Foxworthy, W. A., Meredith, M. A., El Metwally, D., Zhuo, J., . . . Gullapalli, R. P. (2017). Cortical multisensory connectivity is present near birth in humans. *Brain Imaging Behav, 11*(4), 1207-1213. doi:10.1007/s11682-016-9586-6

Takahashi, E., Folkerth, R. D., Galaburda, A. M., Grant, P. E. (2011). Emerging Cerebral Connectivity in the Human Fetal Brain: An MR Tractography Study. *Cerebral Cortex, 22*(2), 455-464.

Toulmin, H., Beckmann, C. F., O'Muircheartaigh, J., Ball, G., Nongena, P., Makropoulos, A., . . . Edwards, A. D. (2015). Specialization and integration of functional thalamocortical connectivity in the human infant. *Proc Natl Acad Sci U S A, 112*(20), 6485-6490. doi:10.1073/pnas.1422638112

van den Heuvel, M. P., Kersbergen, K. J., de Reus, M. A., Keunen, K., Kahn, R. S., Groenendaal, F., . . . Benders, M. J. (2015). The Neonatal Connectome During Preterm Brain Development. *Cereb Cortex, 25*(9), 3000-3013. doi:10.1093/cercor/bhu095

Weiner, K. S., Barnett, M. A., Lorenz, S., Caspers, J., Stigliani, A., Amunts, K., . . . Grill-Spector, K. (2016). The Cytoarchitecture of Domain-specific Regions in Human High-level Visual Cortex. *Cereb Cortex*. doi:10.1093/cercor/bhw361

Weiner, K. S., Golarai, G., Caspers, J., Chuapoco, M. R., Mohlberg, H., Zilles, K., . . . Grill-Spector, K. (2014). The mid-fusiform sulcus: a landmark identifying both cytoarchitectonic and functional divisions of human ventral temporal cortex. *Neuroimage, 84*, 453-465. doi:10.1016/j.neuroimage.2013.08.068