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Fabien Hauw

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Sorbonne Université

École Doctorale Cerveau, Cognition, Comportement (ED3C)

Institut du Cerveau (ICM)

Physiological Investigations of Clinically Normal and Impaired Cognition (PICNIC) lab

Étude comportementale, fonctionnelle et anatomique de la synesthésie des sous-titres

Fabien Hauw

Thèse de doctorat en Neurosciences

Sous la direction de Laurent Cohen

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Devant un jury composé de :

Chotiga Pattamadilok	Université Aix-Marseille	Rapporteure
Julia Simner	Université du Sussex	Rapporteure
Richard Levy	Sorbonne Université	Président de jury
Jonathan Grainger	Université Aix-Marseille	Examineur
Laurent Cohen	Sorbonne Université	Directeur de thèse



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**Behavioral, functional, and anatomical study of tickertape
synesthesia**

Fabien Hauw

Dissertation for the degree of Doctor in Philosophy

Under the supervision of Laurent Cohen

Publicly defended on December 20th, 2023

Before the jury composed of:

Chotiga Pattamadilok	Université Aix-Marseille	Referee
Julia Simner	Université du Sussex	Referee
Richard Levy	Sorbonne Université	President
Jonathan Grainger	Université Aix-Marseille	Examiner
Laurent Cohen	Sorbonne Université	PhD Supervisor

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Résumé

Les réseaux cérébraux impliqués dans le langage oral et le langage écrit sont connectés et interagissent lorsque nous utilisons l'un ou l'autre. Par exemple lorsque nous entendons du langage, nous accédons aux informations concernant l'orthographe de ce que nous entendons, et inversement lorsque nous lisons, nous accédons aux informations phonologiques du contenu. L'aire de la forme visuelle des mots, située dans le gyrus fusiforme gauche, joue un rôle important dans ces interactions. Cette aire est spécialisée dans la reconnaissance des lettres et des mots, et apparaît avec l'apprentissage de la lecture.

La synesthésie est définie comme une « fusion des sens » : la perception dans une modalité sensorielle est accompagnée d'une perception surajoutée, dans une autre modalité sensorielle non sollicitée. Il existe une synesthésie mettant en relation les processus de langages oral et écrit, nommée la synesthésie des sous-titres (tickertape synesthesia, TTS), et dans laquelle la personne perçoit la forme orthographique de ce qu'elle entend. Notre hypothèse était que les régions responsables de la TTS étaient les régions péri-sylviennes impliquées dans le langage, et visuelles impliquées dans le traitement de l'orthographe. Nous avons également prédit que ce phénomène était lié à une activation inverse du réseau de lecture, sous-tendue par des influences descendantes des aires du langage vers les aires de la lecture trop importantes.

Nous avons fait remplir un questionnaire aux personnes ayant cette synesthésie, qui nous a permis de mieux caractériser l'expérience subjective de la TTS, notamment les aspects visuo-spatiaux des sous-titres et le type de stimulus auditif ou la situation pouvant déclencher la TTS. Nous avons aussi montré qu'il existait des différences de performance lors de tests comportementaux. Les synesthètes étaient avantagés lors des tâches impliquant la mémoire de travail orthographique sur stimulation auditive seule, mais n'étaient pas gênés lors de tâche visuelle avec interférence par le biais d'une stimulation auditive concomitante. Nous avons identifié les réseaux neuronaux activés durant la TTS, d'abord chez un seul synesthète, puis nous avons répliqué ces résultats sur tout un groupe. Ces régions correspondent aux régions péri-sylviennes impliquées dans le langage et aux régions occipito-temporales ventrales impliquées dans le traitement orthographique. Les réseaux activés dans la TTS étaient superposables à ceux activés par la lecture. Ces résultats confirmaient donc nos

hypothèses de départ. Nous avons également montré qu'il existait un excès de connectivité au repos chez les synesthètes, notamment entre les régions frontales et occipitales. Il existait aussi un excès de connectivité chez les synesthètes entre les régions auditives primaires et la VWFA lors de l'écoute de langage par rapport au silence. Enfin, nous avons souligné l'importance de cette connectivité fronto-occipitale en étudiant le cas d'un patient atteint d'une cécité corticale suite à des lésions des aires associatives visuelles, avec épargne partielle du cortex visuel primaire. Malgré l'absence de conscience du patient de toute stimulation visuelle, celle-ci activait chez lui une région du cortex visuel primaire. Par rapport aux contrôles, cette région avait une connectivité au repos diminuée avec une région frontale gauche, déjà identifiée comme ayant un rôle dans la prise de conscience de stimuli visuels.

Au total, nos travaux ont permis de mieux caractériser le phénomène de la TTS, et d'en préciser les substrats neuronaux. Ils ont aussi apporté des arguments pour le rôle des régions impliquées dans les modèles actuels du langage et de la lecture.

Abstract

The brain networks involved in speech and written language are connected and interact when we use one or the other. For example, when we hear speech, we access information about the spelling of what we hear, and conversely when we read, we access phonological information about the content. The visual word form area (VWFA), located in the left fusiform gyrus, plays an important role in these interactions. This area is specialized in letter and word recognition, and appears with the learning to read.

Synesthesia is defined as a "fusion of the senses": perception in one sensory modality is accompanied by superadded perception in another, unsolicited sensory modality. There is a synesthesia that links speech and written language processes, called tickertape synesthesia (TTS), in which the person perceives the orthographic form of what he or she hears. Our hypothesis was that the regions responsible for TTS were the perisylvian regions involved in language, and the visual regions involved in spelling processing. We also predicted that this phenomenon was linked to a reverse activation of the reading network, underpinned by top-down influences from language areas to reading areas that were too strong.

We explored this synesthesia through a series of complementary studies. We administered a questionnaire to people with this synesthesia, which enabled us to better characterize the subjective experience of TTS, including the visuo-spatial aspects of subtitles and the type of auditory stimulus or situation that can trigger TTS. We also showed that there were differences in performance on behavioral tests. Synesthetes had an advantage on tasks involving orthographic working memory on auditory stimulation alone, but were not impaired on visual tasks with interference via concomitant auditory stimulation. We identified the neural networks activated during TTS, first in a single synesthete, and then replicated these results across an entire group. These regions correspond to the perisylvian regions involved in language and the ventral occipitotemporal regions involved in orthographic processing. The networks activated in TTS were overlapped with those activated by reading. These results thus confirmed our initial hypotheses. We also showed that there was an excess of connectivity at rest in synesthetes, notably between the frontal and occipital regions. There was also an excess of connectivity in synesthetes between primary auditory regions and the VWFA during language listening compared with silence.

Finally, we highlighted the importance of this fronto-occipital connectivity by studying the case of a patient with cortical blindness following lesions of the visual associative areas, with partial sparing of the primary visual cortex. Despite the patient's lack of awareness of any visual stimulation, it activated a region of the primary visual cortex. Compared with controls, this region had diminished resting connectivity with a left frontal region, already identified as having a role in awareness of visual stimuli.

In summary, our work has enabled us to better characterize the phenomenon of TTS, and to clarify its neural substrates. It has also provided arguments for the role of the regions involved in current models of language and reading.

List of frequently used abbreviations

EBA, Extrastriate body area

FFA, Fusiform face area

IFG, Inferior frontal gyrus

MRI, Magnetic Resonance Imaging

MTG, Middle temporal gyrus

MVPA, Multivariate pattern analysis

OFA, Occipital face area

PPA, Parahippocampal place area

SMA, Supplementary motor area

SMG, Supra-marginal gyrus

STG, Superior temporal gyrus

STS, Superior temporal sulcus

TMS, transcranial magnetic stimulation

TTS, Tickertape synesthesia

vOTC, ventral occipito-temporal cortex

VWFA, Visual Word Form Area

Publications

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1. Hauw, F., El Soudany, M., & Cohen, L. (2022). Subtitled speech: Phenomenology of tickertape synesthesia. *Cortex*. doi: 10.1016/j.cortex.2022.11.005.
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"Seeing someone reading gives rise in my mind to a curious metonymy in which the reader's identity takes on the color of the book and that of the setting in which it is read."

- Alberto Menguel

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General introduction

The emergence of writing in the 4th millennium BC opened an era of intricate relationships between vision and language (Nissen, 1985). In the past, it was common practice to read aloud, for deciphering texts and grasping their meaning through orality (Crosby, 1936). Silent reading emerged more recently, mainly in a religious context, where the written word played a crucial role in terms of preservation and memorization. As a side effect, silent reading was also perceived as intellectually and morally dangerous. Reading aloud has continued to play an important role, particularly in group readings. This was partly due to the low literacy rates that prevailed in premodern societies, until the advent of the printing press. In those days, public reading was the simplest way of sharing the contents of a book.

Despite its preponderant role today, it is important to emphasize that reading is too recent for a brain area to have been dedicated to it by evolutionary pressure. However, with the right teaching, we can learn to read in late infancy - an essential prerequisite for the acquisition of future knowledge.

It is fascinating that our brains can extract complex concepts, meanings and ideas from simple geometric shapes and lines. When we read, in a fraction of a second, we can ignore seemingly major physical variations: for example, between an "A" and an "a", which we interpret in the same way; while at the same time we pay close attention to other seemingly minor physical variations: for example, between a "c" and an "o". On the contrary, in an unfamiliar alphabet, the importance of these differences tends to be reversed. How is our brain able to instantly grasp these nuances while ignoring others? How can we determine that a particular character belongs to an alphabet we know, while another, almost identical but slightly different geometrically, does not? How can such seemingly complex rules be assimilated so early in our learning process, without a brain mechanism dedicated to the task? Finally, given the close relationship between speech and the reading process, what is the specific role of speech in this dynamic? These are captivating questions that invite us to explore the deep mechanisms of our brains when it comes to reading and comprehension.

In this work, we study reading and its links with speech through tickertape synesthesia (TTS), an atypical condition in which synesthetes see in their mind's eye the written form of the words that they are hearing, and do so automatically and involuntarily. This synesthesia is

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characterized by a stronger link between speech perception and orthography than in the neurotypical population. As a background to our work, we will review in the introduction some general notions on language and reading.

First, we will consider the reading and speech processes, as studied through behavioral methods. We will then review their anatomical correlates: which are the regions involved in orthographic and language processing, and which of them are the source of the behavioral phenomena described before. We will also show that the left occipitotemporal cortex, and specifically the Visual Word Form Area, is involved in the perception of written words, but also plays a role in interfacing auditory and visual language processing. Finally, we will review some of the current models of reading and speech processing.

Secondly, we'll take a brief look at reading disorders, including developmental and acquired dyslexias.

The third part of the introduction will present synesthesia in general, its current accounts, its etiological factors and anatomical correlates.

Finally, we will present the limited literature relative to tickertape synesthesia, which is mainly descriptive and phenomenological.

1. Reading and speech

A. Behavioral effects in language

i. During reading

During reading, a multitude of parameters influence (or paradoxically do not influence) the way we identify and read words. Some can be consciously apprehended, while others are subtle enough to remain subliminal. A great deal of research has therefore been carried out into what these parameters are, and what impact they have on performance - an impact which may itself vary according to the task being performed.

Low-level properties

Visual characteristics. Paradoxically, certain major physical characteristics of a word do not influence its identification. The most striking example concerns case (Rayner and Pollatsek, 2013): we read "RAGE" and "rage" in the same way, yet, between lower and upper case, no two letters of this word are alike. However, case alternation, FoR eXaMpLe iN tHiS wAy, disturbs word identification in some tasks (Coltheart and Freeman, 1974; Humphreys et al., 2003), but has no impact in others (Smith et al., 1969). Nor does the **font** impact our ability to identify a word (Rayner and Pollatsek, 2013), we don't differentiate between "rage" and "rage", although we may be used to some fonts rather than others and therefore be bothered when reading a new atypical font. There are other characteristics of letters that we know how to ignore when it comes to identifying a word. If it's written in **bold** or **italics**, there's no impact on its identification either, and the same goes for font size (to some extent), although variations in font size can impact reading speed (for review, see (pour revue, voir Legge and Bigelow, 2011; Rudnicky and Kolers, 1984; Sanocki, 1991), but with no impact on comprehension (Tavakoli and Kheirzadeh, 2011).

Spatial organization of letters. Other physical properties of a stimulus will hinder its identification without modification of the letter. This is the case when letters are **rotated**, with reading time increasing the greater the rotation (Blythe et al., 2019; Risko et al., 2014), although identification of an isolated letter is not disrupted (Corballis et al., 1978). Reading is also disrupted when there is too much **spacing** between letters (Marzouki and Grainger, 2014), particularly beyond 2 spaces (Vinckier et al., 2011), the discomfort being mainly related to letter eccentricity.

Priming effects

Other subliminal effects, on the other hand, have a behavioral influence, notably **priming effects**. Indeed, a lexical decision task is facilitated when the same word has been presented subliminally as a masked prime just before (Forster and Davis, 1984), but priming has no effect when the target is a pseudoword. The **transposition of letters** does not seem to interfere with the identification of the original word. Indeed, a prime with transposed letters becomes a pseudoword and tends to be mistaken for the original word in lexical decision tasks (Chambers, 1979). When using words with transposed letters, masked priming effects are

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similar, whether adjacent (Forster et al., 1987; Perea et al., 2003) or non-adjacent (Perea and Lupker, 2004) letters are transposed within the prime. It should be noted that the results obtained with transposition of letter(s) run counter to certain models of word identification (Grainger and Jacobs, 1996; McClelland and Rumelhart, 1981), which stipulate that the position of a letter in a word is encoded. When the prime differs from the target word by just one letter (e.g., the target "hear" for the prime "HEOR"), i.e., when there is orthographic similarity, there is an **orthographic priming effect** (Perfetti et al., 1988) in a target detection task. In the same task, the authors also noted a **phonological priming effect**: performance was also improved when the prime was a pseudo-homophone (e.g., the target "made" for the prime "MAYD"). On the contrary, other authors (Humphreys et al., 1982) with a target detection task, report a phonological priming effect when the primer is a homophone (e.g., in English the target "made" for the primer "maid"), but not when it is a pseudo-homophone (e.g., in English the target "brain" for the primer "brane"). Finally, there are also **semantic priming effects**: when the word "nurse" is subliminally presented and the target word is "doctor", the lexical decision is simpler (Perea and Rosa, 2002), even when the letters of the primer are transposed (Perea and Lupker, 2003).

Lexical effects

Orthographic neighbors. Other effects are less clear-cut, with variable results, including the orthographic neighbor effect. An orthographic neighbor is defined as a word sharing the same letters except for one (Coltheart et al., 1979). Older studies show a facilitating effect of the number of orthographic neighbors in a lexical decision task (Andrews, 1992, 1989), while other studies show that the number of orthographic neighbors correlates with longer response times in the same lexical decision task (Grainger, 1990). On the other hand, it generally has a facilitating effect on naming tasks.

Regularity effect. In reading aloud tasks, but not in lexical decision tasks, there can be a word regularity effect: irregularly spelled words are read more slowly (Seidenberg et al., 1984). This impact of a word's orthographic irregularity depends on the **position of the irregularity**: its position at the beginning of the word has a greater impact on naming than if it is at the end of the word (Coltheart and Rastle, 1994; Cortese, 1998).

Word superiority effect. We also know that a letter is more easily recognized when presented within a real word than in isolation or in an unpronounceable letter sequence: this is the word superiority effect (Johnston and McClelland, 1973; Reicher, 1969). This is also the case for the recognition of a letter within a pseudoword versus an unpronounceable letter sequence (Baron and Thurston, 1973). Letter identification remains easier when presented integrated within a word than within a pseudoword (Grainger et al., 2003).

Lexical effect. In a reading lexical decision task, responses are longer when the stimulus is a pseudoword than when it is a word (Forster and Bednall, 1976). In a read-aloud task, reaction times are also longer for pseudowords than for low-frequency words, which themselves take longer to identify than high-frequency words (Ferrand and New, 2003).

Other effects

Frequency effect. There are also effects of word **lexical frequency** on error rates and reaction times (Allen et al., 1995; Ferrand and New, 2003; Grainger, 1990; Monsell et al., 1989), with more frequent words being more easily processed. These effects are more controversial for the **bigram frequency**: there is no impact of bigram frequency on lexical decision task (Andrews, 1992; Schmalz and Mulatti, 2017), while there is on naming latencies, with a greater effect for low- than high-frequency words (Andrews, 1992; Rice and Robinson, 1975; Schmalz and Mulatti, 2017). These results suggest that bigram frequency would have an impact in tasks where words need to be pronounced. Word **syllable frequency** also influences response time and accuracy during lexical decision tasks with visual presentation (Carreiras et al., 1993; Conrad et al., 2007), although this effect may depend on the language tested, since in English the results seem to be the opposite (Macizo and Van Petten, 2007).

Length effect. The orthographic length of a word or pseudoword is correlated with response times in the lexical decision task, whereas this correlation is only present for pseudowords in the read-aloud task (Juphard et al., 2004). This orthographic length also impacts word recall, with shorter words being more difficult to recall in immediate recall tests (Baddeley et al., 1975), although it is possible that this effect on working memory is ultimately related to the lexical properties of words, such as the number of orthographic neighbors for example (Jalbert et al., 2011). The **number of syllables** in a word lengthens the time needed to identify and name a very low-frequency word or pseudoword, whereas in lexical decision it is only present

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for very low-frequency words (Ferrand and New, 2003). Finally, the **number of phonemes** is inversely correlated with word identification time (Rey et al., 1998).

In total, many sub-lexical and lexical effects during reading were studied in various tasks. These have led to the development of several models, which we shall see later, but also to the criticism or increased validation of some of them.

ii. During speech

There are also numerous behavioral effects described during speech perception.

Orthograph influence

Orthographic consistency effect. In an auditory lexical decision task, participants are less precise and slower for words in which a part has several possible spellings (e.g., in French, in the word "plomb", "-omb" can be written as in "nom", "tronc", "long", etc.; Ziegler and Ferrand, 1998). The same applies to pseudowords containing a syllable that can be written in different ways (Ventura et al., 2007). This effect seems to be linked to the networks in charge of phonological processing, since transcranial magnetic stimulation (TMS) stimulation of these areas abolishes the advantage of words with only one possible spelling (Pattamadilok et al., 2010).

Orthographic priming. Orthographic priming can occur when stimuli are presented auditorily. The facilitative effect is then greater in lexical decision tasks when the stimulus presents an orthographic similarity with the target word (Chéreau et al., 2007).

Facilitation on lexical decision. In a lexical decision task on one-syllable words or pseudowords, the decision is facilitated if the word preceding the target is orthographically and phonologically similar to the target (e.g. in French "jouer" then "joue"), but not if only one of these aspects is similar (Jakimik et al., 1985).

Effect of orthographic neighbors. The density of a word's orthographic neighborhood affects lexical decision, with faster reaction times for words with a greater number of orthographic neighbors (Ziegler et al., 2003; Ziegler and Muneaux, 2007).

Effect on rhyme judgment. In a rhyme judgment task, Seidenberg and Tanenhaus (1979) showed that response times were shorter when words rhymed and had similar spellings (e.g.

in French "seau" and "peau") than when they rhymed but with different spellings (e.g. "seau" and "chaud").

Taken together, these results suggest ongoing interactions between orthographic and phonological processing during speech perception, and hence the existence of neural networks linking these two systems.

Other effects

Lexical influence. In letter recognition tasks involving phonetically ambiguous auditory stimuli (e.g. between a [d] and a [t] followed by "-est", in one case forming the word "test" and in the other the pseudoword "dest"), there is a **lexical effect** (sometimes called the "**Ganon effect**"): the letter recognized more often corresponds to that found in the real word compared to that in the pseudoword (Bidelman et al., 2021; Connine and Clifton, 1987; Ganong, 1980).

Influence of word and syllable frequency. González-Alvarez and Palomar-García (2016) showed with an auditory lexical decision task that there was an effect of word frequency, with participants being faster for more frequent words. On the other hand, similar to what is seen in visual modality, participants were slower for words with a more frequent first syllable. The former effect can be explained by the fact that words with a high lexical frequency have a higher lexical representation, as they are encountered more frequently. The later effect may be linked to competition between words beginning with the same syllable.

Phonological neighbor effect. In auditory modality, a neighbor is defined as a phonologically similar word, the degree of similarity depending on the number of differing phonemes. The presence of many neighboring words (the neighborhood density) and the lexical frequency of these neighbors (the neighborhood frequency) could have an impact on the lexical decision. Indeed, when neighbor frequency is low (independently of neighbor density), classification is faster and more accurate, whereas it is slower but more accurate when neighbor density is high (independently of neighbor frequency, Luce and Pisoni, 1998). Dufour and colleagues (2013) showed an effect of neighborhood density only on response accuracy, with a higher error rate for words with high neighborhood density. The previously mentioned frequency effect could in fact be dependent on neighborhood frequency, i.e., a high frequency of neighboring words. Influences of the phonological neighborhood on the lexical decision also suggest competition between similar words during lexical processing in word listening.

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Phonological priming effect. There is a facilitating effect of phonological overlap, when a monosyllabic primer and its target share the first phonemes (Dufour and Peereman, 2004), which remains valid when the prime is disyllabic only for high lexical frequency targets.

Semantic priming effect. Daltrozzo and colleagues (2011) took the semantic priming protocols already studied in visual presentation and used them on a lexical decision task in auditory modality. They showed that slower participants responded faster when the priming was semantically related to the target.

iii. Synthesis and interactions

There are several properties and effects that influence performance in both reading and speech listening. We note that some properties are not constant across studies, and that this may depend on many factors, such as the language used, the task involved, the definitions of parameters used by the authors, etc.

These effects have more or less perceptible repercussions under ecological conditions, and some are mainly observed under specific experimental conditions. This is the case of priming effects during reading or listening to language, which have no ecological equivalent, but which highlight interactive processes between orthographic and phonological processing on the one hand, but also between processing levels (sub-lexical, lexical and semantic) on the other.

Other mentioned effects also show that there are important interactions between orthographic and phonological systems. This is obviously the case for all the orthographic effects reported in auditory modality experiments, but it is also the case for the influences of phoneme and syllable features during visual stimulation. Indeed, these interactions are paramount in learning to read (Bentin and Leshem, 1993; Dehaene, 2011; Gough et al., 2017), and their disruption may instead be associated with reading disorders (Snowling, 1980). They are also crucial when learning new languages (Hayes-Harb and Barrios, 2021; Sparks and Miller, 2000), or when perceiving new words - pseudowords (Tunmer and Nesdale, 1982), in order to deduce a pronunciation from spelling, and vice versa. These interactions, as well as the various properties influencing reading, must therefore be considered when developing models.

B. Anatomical correlates of language

i. Activations during reading

Visual word form area

As we saw earlier, the appearance of reading on the scale of our history is too recent to have exerted any evolutionary influence on our genome. However, after alphabetization, a region activated during reading was found in the left fusiform gyrus. This region has been named the Visual Word Form Area (VWFA, Cohen et al., 2000, **Figure 1.1**), word form being defined as the sequence of letters making up the word (Warrington and Shallice, 1980).

Figure 1.1

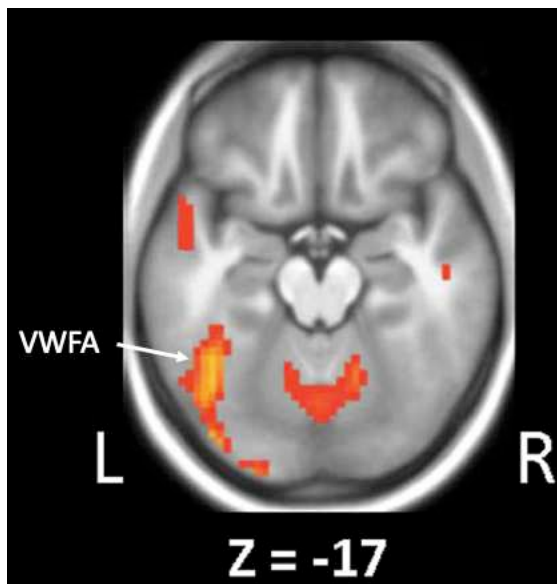


Figure 1.1. Activations in participants when reading. Adapted from Bouhali et al. 2014.

This area is defined in each individual as being more activated for orthographic stimuli than for other types of visual stimuli (faces, houses, tools, words) within the left fusiform gyrus. It has subsequently been shown in various studies and meta-analyses that the localization of this region is systematically reproducible between subjects (Bolger et al., 2005; Dehaene et al., 2002; Jobard et al., 2003).

However, the peak coordinates of this region can vary significantly from person to person. Indeed, when looking at coordinates selected across a group of individuals, the selectivity of the VWFA for orthographic versus non-orthographic stimuli is discussed (Kherif et al., 2011;

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Vogel et al., 2014, 2012), mainly due to this inter-individual variability. On the contrary, when we look at the activations of this same region, but at the coordinates identified in each individual, we find selectivity for orthographic stimuli (Glezer and Riesenhuber, 2013). The problem of this inter-individual variability and its consequences for group analyses is addressed in work on reading (Li et al., 2023; Lipkin et al., 2022), but also more generally in functional MRI studies (Seghier and Price, 2016). One solution could be to cross-reference individual activations selected according to certain criteria that may vary, with regions of interest from atlases, previous studies (Li et al., 2023) or functional probability atlases (Lipkin et al., 2022).

Other regions activated during reading

The left superior temporal gyrus (STG). Along with the visual cortex, this was one of the first regions whose activation during reading aloud was demonstrated by PET (Positron Emission Tomography; Howard et al., 1992). It was subsequently shown that the STG was activated more by pronounceable words than by strings of consonants (Bavelier et al., 1997), and its role would therefore be the phonological representation of words (Price and Binder, 2001). Other studies have shown that this region plays a role in semantic processing (Booth et al., 2006; Vandenberghe et al., 1996). Matsumoto and colleagues (2005) also showed a repetition-suppression effect (repetition-suppression corresponds to a decrease in the activation of a given region during the second successive presentation of the same stimulus) in the STG during semantic priming. In the same study, the N400 wave linked to the semantic priming effect in EEG correlated with the repetition-suppression effect in the left STG, reinforcing the idea of its role in semantic processing, which would subsequently modify the phonological representation of the word.

The left angular gyrus. In 1996, Menard and colleagues also showed, with PET, greater activation for written words than for other visual categories in the left angular gyrus. As for the STG, Vandenberghe and colleagues (1996) finally showed a rather semantic role for this region. The angular gyrus may also be involved in the integration of contextual information during reading (Branzi et al., 2021). In this study, the authors applied TMS to this region during a reading task with semantic integration of two paragraphs, one providing context, the second

target information. TMS was applied after reading the contextual paragraph and disrupted the recall task, without disturbing reading.

The left middle temporal gyrus (MTG). Some studies attribute to the left MTG a role in semantic information processing (Davey et al., 2016; Price et al., 1997), as does the temporo-polar region (Lambon Ralph et al., 2009). Booth and colleagues (2006) also showed that the left MTG was more activated during a semantic task than during a phonological rhyme-judgment task. This region is also involved in lexical processing. It is more activated during word reading than pseudoword reading (J.S. Taylor et al., 2013), although this property is task-dependent (McNorgan et al., 2015). Multivariate analyses, meanwhile, highlighted the fact that the left MTG showed different activation patterns depending on the lexicality of the stimulus (word vs. pseudoword; Baeck et al., 2015; Fedorenko et al., 2012).

The left supramarginal gyrus (SMG). It may be involved in the phonological processing of reading (Price et al., 1997), complementing the results of imaging studies on speech (Buchsbaum et al., 2005a; Démonet et al., 1994). It is thought to be used to retrieve word pronunciation during reading (Stoeckel et al., 2009) and is also involved in non-lexical, pseudoword reading. Indeed, with intraoperative cortical stimulation of the left SMG, (Roux et al., 2012) showed a disturbance in the reading of pseudowords but not irregular words (irregular words are words which do not meet the standards of grapheme-phoneme translations, e.g. in French "oignon" or "yacht"), further supporting its role as a grapheme-phoneme translator. The application of TMS to the SMG also influences performance on phonological tasks but has no impact on semantic tasks (Magdalena W. Sliwinska et al., 2015).

Left inferior frontal gyrus. This appears to play a role in semantic processing: in a semantic priming task, the priming is responsible for a repetition-suppression effect in the left inferior frontal gyrus (Matsumoto et al., 2005). The ventral part of the left inferior frontal gyrus is also more activated in a semantic task than in a rhyme judgment task, whereas its dorsal part is more activated in the rhyme judgment task (Booth et al., 2006; Poldrack et al., 1999). Finally, the left inferior frontal gyrus is thought to be involved in the syntactic aspect of reading (Keller, 2001).

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ii. VWFA properties

We know that the VWFA is activated preferentially by **orthographic stimuli** than by visual stimuli from other categories, but we also know that within this visual category, a number of parameters influence the activation of this area.

Influences of pre-lexical characteristics

Case. The masked presentation of a stimulus in upper or lower case, followed by the conscious presentation of the same stimulus, produces a repetition-suppression effect, regardless of whether the stimulus was presented in the same case in both cases (Dehaene et al., 2001).

Mirror effect. Recognizing an animal or tool in its mirror version is possible (Biederman and Cooper, 1991; Dehaene et al., 2010a; Eger et al., 2004; Tarr and Pinker, 1989) and even essential for survival from an evolutionary point of view: we need to be able to recognize a threat when it presents itself in one profile as in another. However, this property does not apply to words (Dehaene et al., 2010a). For letters, it is essential to be able to discriminate them when they are presented in mirror image (Pegado et al., 2011). Indeed, it is essential to be able to differentiate a "b" from a "d", or a "p" from a "q", at the risk of changing the meaning of a word. There is therefore an inhibition of this mirror effect when learning to read (Pegado et al., 2014, 2013). The persistence of this mirror effect for certain letters could be involved in certain types of dyslexia (Corballis, 2018; Lachmann and Van Leeuwen, 2007).

Style. Nor does the style of handwriting, handwritten or printed, influence word recognition. Indeed, the same repetition-suppression effect is also present when the prime and target stimulus are presented in printed form for the former and in handwritten form for the latter; on the contrary, there is a repetition-enhancement effect (during the second successive presentation of the same stimulus, activation of a given region is greater than during the first presentation), when the prime is handwritten and the target word printed (Qiao et al., 2010).

Orthographic similarity. The VWFA is sensitive to the orthographic similarity of 2 stimuli (regardless of whether they are words or pseudowords), and the fewer letters the stimuli differ in number, the more similarly it activates (Baeck et al., 2015).

Spacing and rotation. Letter spacing and word rotation also influence VWFA activation. Beyond 45° of rotation and 2 spaces between characters, activations within the left ventral

occipito-temporal cortex (vOTC) are greater (Cohen et al., 2008), suggesting a shift to serial letter reading, and a disruption of bigram formation. These results concur with those of Vinckier et al. (2011), who also reported a threshold of 2 spaces between 2 characters, beyond which reading performance deteriorates.

Effect of letter order and location. Dehaene et al. (2004), using circular anagrams (where the passage of a letter from the beginning to the end or the opposite changes the meaning of the word, e.g. "REFLET" → "TREFLE"), showed that there was a repetition-suppression effect in a **posterior part** of the VWFA for a word followed by its anagram only when the second was presented at a position visually offset by one letter, i.e. when the same letter was presented at the same location. In contrast, a more **anterior region** showed this repetition-suppression effect only when the second stimulus was identical to the first, regardless of location in the visual field. These results therefore suggest that the posterior region is sensitive to a letter in a specific, fixed location, whereas the more anterior region is not influenced by location in the visual field and recognizes the same stimulus regardless of its location. These results concur with those of Cohen and colleagues (2002), who showed that the VWFA activates at the same location, regardless of the stimulus location, in this case whether it was in the right or left visual hemifield in their study.

Influences of lexical characteristics

Lexical frequency. The VWFA is also sensitive to certain lexical properties of words. For example, it is known to be sensitive to the lexical frequency effect of the perceived word: it activates less for high lexical frequency words than for low lexical frequency words (Kronbichler et al., 2004; Schuster et al., 2016; White et al., 2019). Other occipitotemporal regions have also been shown to be sensitive to the frequency effect, with greater activations for low- than high-frequency lexical words in these regions (Keller, 2001; Kuo et al., 2003).

Lexical effect: divergent results. In their study, Kronbichler et al. (2004) also show greater activation in the VWFA for pseudowords than for words, thus demonstrating a lexicality effect. These findings are consistent with the results of another review of nine studies, 6 of which showed similar activation differences at or near the VWFA (Mechelli et al., 2003). On the contrary, other studies show greater activation for words than for pseudowords. Lerma-Usabiaga et al. (2018) finds this effect in an anterior region of vOTC, thought to be connected

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to language regions, with a simple detection task. In contrast, Binder et al. (2003) and Fiebach et al. (2002) used a lexical decision task, whereas in Kronbichler's study, participants had to silently read the stimuli. This difference in task could partly explain the opposite results. In addition to differences in activation intensity, we can also look at the pattern of activation. With **multivariate pattern analysis** (MVPA), we can train a decoder to recognize certain activation patterns, appearing for a given experimental condition, and then test it on these same conditions. Stevens et al. (2017), using this type of analysis, showed that within the VWFA, activation patterns were different for words and pseudowords, reflecting a lexical effect.

iii. Multimodal role of the VWFA

The VWFA is therefore activated when orthographic stimuli are perceived, but what about during reading through other modalities? It seems that visual stimulation is not essential to elicit preferential activation of this region for orthographic stimuli.

Braille activation. This property has been studied mainly in people with congenital blindness. Firstly, it was shown that the VWFA was also activated during Braille reading in **congenitally blind people** (Kim et al., 2017; Reich et al., 2011), at the VWFA's usual coordinates (**Figure 1.2**). Siuda-Krzywicka and colleagues (2016) showed that in **sighted people**, after learning Braille, Braille reading also activated the VWFA. In this study, the authors also reported, after Braille learning, an increase in VWFA resting connectivity with somatosensory cortex and a decrease with visual areas and motor cortex. More recently, Matuszewski and colleagues (2021) have also shown activations of the VWFA when reading Braille after learning it in sighted people. In people with **acquired blindness**, these activations are also found after Braille learning (Burton and McLaren, 2006). Visual deprivation alone could be responsible for the reorganization of the visual cortex, but this cortical remodeling can also occur in the absence of visual deprivation (Bola et al., 2016).

Activation through sensory substitution systems. These activations of the VWFA without visual stimulation are not limited to Braille. Striem-Amit et al. (2012) trained people with congenital blindness to read using a visual-to-auditory sensory-substitution system. This system converts images into "auditory landscapes", enabling extraction of visual information from these auditory stimuli. In congenitally blind subjects, sounds corresponding to letters

activated the VWFA more intensely than sounds corresponding to the other visual categories used.

Activation during auditory stimulation. Finally, we also know that the VWFA is activated during lexical decision tasks in auditory modality (Dehaene et al., 2010b) or during rhyme judgment tasks (Yoncheva et al., 2010). On the contrary, other studies have shown that it was not activated during passive listening or phoneme or letter detection (Cohen et al., 2004; Dehaene et al., 2002). Selective attention therefore seems to influence VWFA activation during auditory tasks (Cohen et al., 2021; Yoncheva et al., 2010). However, the presence of the left fusiform gyrus is not essential for the performance of certain tasks during language listening (Tsapkini and Rapp, 2010), whereas its lesion will classically result in pure alexia (Cohen et al., 2016).

Figure 1.2

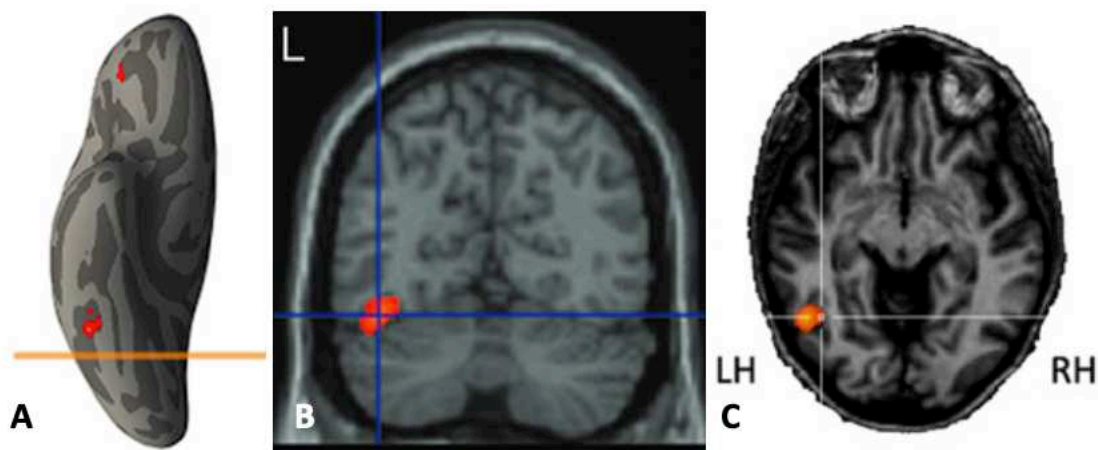


Figure 1.2. (A) Inferior view of the inflated left surface, with activation of the VWFA (MNI -43 45 -13) while touching Braille words > tactile controls (Kim et al., 2017); (B) Coronal view with activation of the VWFA (MNI-42 64 -16) during a rhyme judgment task > melodic matching task (Yoncheva et al., 2010); (C) Axial view with activation of the VWFA (MNI -51 -58 -9) during letter perception vs other categories through sensory substitution device (Striem-Amit et al., 2012).

Altogether, these findings suggest that the VWFA may have a higher-level role in language processing and not be specific to reading (Kim et al., 2017). It activates in the absence of visual

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stimuli, in response to Braille, or to auditory stimuli, and may have a multi-modal integration role (Cathy J. Price, 2012) through its top-down connexions.

iv. VWFA development and brain plasticity

Neuroplasticity. This is a well-studied phenomenon that refers to the brain's ability to alter its molecular, synaptic, structural, and functional organization, in response to the acquisition of new skills, during normal development or consequently to a central or peripheral injury, or chronic disease (for review, see Cramer et al., 2011). Several studies have reported structural and functional changes following the learning of new skills (for reviews see Dayan and Cohen, 2011; Li et al., 2014). MRI reflection of plasticity may be secondary to long-term exposure or training (Boyke et al., 2008; Maguire et al., 2000), but plasticity can also rapidly be visible, with some structural changes even appearing after only a few hours of learning (Sagi et al., 2012).

Neural recycling hypothesis. As previously stated, the emergence of reading is too recent in human history, and it is therefore impossible for evolutionary pressure to have dedicated a brain region to this function. However, in a stable and reproducible manner, a region of the left fusiform gyrus is activated when orthographic stimuli are perceived. The main hypothesis is that of neural recycling (S. Dehaene and Cohen, 2007). According to this hypothesis, during the acquisition of new skills, cortical regions initially dedicated to another process are "recycled" and become specialized for the new skill. The plasticity of these regions is important to enable remodeling. Moreover, the previous organization of these regions does not disappear, and old connections and anatomical constraints influence the reorganization.

Recycling of the fusiform gyrus. The choice of these regions is not random and depends on the characteristics of the neurons and their connections to other brain regions. There are two reasons for this localization of specialization in word recognition, which are not mutually exclusive. Firstly, the localization of the region must exhibit sensitivity to the physical characteristics of the stimulus ("the **shape hypothesis**"; Hannagan et al., 2015). Neurons in the left fusiform gyrus are known to be specialized in the detection of shapes and details, even prior to learning to read. For example, it seems that the VWFA is particularly sensitive to the physical aspects characterizing letters such as line junctions (Szwed et al., 2011). It is also sensitive to stimuli in foveal position which enables fine discrimination of perceived objects (Hasson et al., 2002) and is also sensitive to high spatial frequencies (Woodhead et al., 2011).

Secondly, the region must also be connected to other cortical regions involved in task processing ("the **biased-connectivity hypothesis**"; Hannagan et al., 2015). This is the case for the left fusiform gyrus, which is a region structurally connected to the left perisylvian language regions (Bouhali et al., 2014; Epelbaum et al., 2008) via the arcuate fasciculus (Yeatman et al., 2011) and the posterior part of the corpus callosum (Wandell, 2011; for review see Wandell et al., 2012). Further resting-state functional connectivity analyses have also shown the VWFA to be more connected to the left temporal cortex and left inferior frontal gyrus (Abboud et al., 2015), including in neonates (Li et al., 2020). Saygin and colleagues (2016) also demonstrated that it was possible to determine where the VWFA would be located in children from vOTC structural connectivity data acquired 3 years earlier, prior to reading acquisition. Moulton et collaborateurs (2019) also showed that prior to this learning, the future location of the VWFA depended on connections to left inferior parietal regions, playing a key role in early literacy in letter-to-letter reading and attentional control. In the context of other domains, diffusion MRI studies have shown that the specialization of a region for a given domain is related to its structural connectivity, and particularly to other regions also involved in that domain (for review see Mahon and Caramazza, 2011; Osher et al., 2016; Saygin et al., 2012).

Neuronal recycling, a dynamic and permanent phenomenon. This neuroplasticity is not limited to the peri-natal period or to childhood. Indeed, it is well studied in **stroke recovery** or in the aftermath of **brain injury** (Dimyan and Cohen, 2011; Levin, 2003; Su et al., 2016). However, the acquisition of new skills such as reading, even in **adulthood**, is also responsible for neuroplasticity. Striem-Amit et al. (2012), with their **sensory substitution device** previously described, showed that after training the VWFA became more active for sounds corresponding to letters than for those corresponding to other visual categories. Similarly, when activations are compared before and after learning to read in non-readers at a late age, we observe the emergence of a specialization of the VWFA for orthographic stimuli, which did not exist before (Dehaene et al., 2010b). Other arguments in favor of neuronal recycling in occipital regions in later life come from studies of people with **acquired blindness**. In these people, reading Braille after learning it activates the VWFA (Burton and McLaren, 2006). These plasticity phenomena can also occur transiently and reversibly. Indeed, Merabet and colleagues (2008) showed that after **visual deprivation** lasting several days, activations appeared in the occipital cortex in response to tactile stimulation, and regressed on a new

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MRI 24 hours once the deprivation had been lifted. Finally, in the context of the LCD model hypothesis, the organization of vOTC would be like that found in primates (Booth, 1998), with modules parameterized to recognize simple shapes. Our writing systems would therefore have adapted to the elementary shapes that our visual system is already able to recognize, making them easier to learn (S. Dehaene and Cohen, 2007). The emergence of regional specialization is an argument in favor of neural recycling.

Functional role of the left fusiform gyrus prior to reading. Comparing the categorical specialization of vOTC in literate and illiterate individuals, it appears that specialization for words develops in a region previously specialized for faces (Dehaene et al., 2010b), thus causing a contralateral, rightward shift of this region specialized for faces. Saygin and colleagues (2016), however, showed that there was no preference for faces at the location of the future VWFA in non-literate children. Finally, another study showed that this region was specialized for tools before reading acquisition (Dehaene-Lambertz et al., 2018), and that the region specialized for processing faces was indeed present nearby. In the end, it looks that the VWFA develops in a region without specialization, close to the one specialized for faces, thus blocking its development, and thus constraining the migration of this specialization to the right hemisphere (Feng et al., 2022).

Taken together, these results suggest that the region where the VWFA develops is highly plastic, in a way that lasts throughout life, and lends support to the neuronal recycling hypothesis.

Genetic and environmental influences. Finally, the acquisition and development of reading skills is influenced by environmental and genetic factors. Indeed, twin studies have shown significant heritability of reading skills, both with (DeFries et al., 1987; DeFries and Gillis, 1993) and without reading difficulties (Harlaar et al., 2005a, 2007). There is a genetic influence before school entry on phonological awareness and naming (Byrne et al., 2006), which is maintained until the elementary grades (Byrne et al., 2009).

There are also environmental factors such as smoking during pregnancy, complicated childbirth or birth weight (Mascheretti et al., 2018) that influence reading performance. Finally, there are interactions between these 2 factors, whose influence seems to be moderated by the parents' socio-educational level (Friend et al., 2008).

v. Activations during speech

Parallel to reading, speech processing involves identifying phonological sequences, and then extracting lexical and semantic information from sounds. Several regions are involved in these successive stages.

Regions involved in speech processing

The primary auditory cortex. Language recognition begins with perception. The primary auditory cortex analyzes all auditory information, both language and non-language, and occupies the two STG (Liegeois-Chauvel et al., 1991). It is also a region activated by the inner voice (Alderson-Day et al., 2016; Shergill et al., 2002).

STG and posterior left superior temporal sulcus (STS). Sounds are then processed phonologically. When they are phonologically intelligible, according to some authors the information then diffuses to the posterior regions of the STS (Benson et al., 2006; Narain, 2003), although other studies report diffusion to the more anterior parts of the left STG and STS (Scott, 2000; Scott et al., 2006). Finally, it seems that the more anterior regions are linked to the processing of acoustic features of the stimulus (Binder et al., 2004; Leaver and Rauschecker, 2010; Obleser et al., 2006).

Left anterior STS. This region appears to play a role in syntactic processing and lexical-semantic recognition. Initially, it was assumed that this region played a lexical-semantic role (Giraud and Price, 2001), with greater activation for words than for pseudowords. Humphries and colleagues (2001) describe greater activation for sentence processing, suggesting a syntactic role, which appears to extend to the left temporopolar (Pallier et al., 2011).

Left inferior parietal regions. The **left SMG** has several functions in speech. Its main role appears to be related to phonological language processing in various aspects. For example, it is involved in auditory-motor correspondence for language production (Hickok and Poeppel, 2015), phonological working memory (Buchsbaum et al., 2005a; Buchsbaum and D'Esposito, 2008; Strand et al., 2008), and also in phoneme-grapheme correspondence during learning to read (Dehaene-Lambertz et al., 2018), in a transient manner. Moser and colleagues (2009) also report left inferior parietal activations during syllable order judgment tasks. In the **angular**

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gyrus, activations related to semantic access are also reported (Binder et al., 2009; Homae, 2002), notably during lexical decision tasks (Raettig and Kotz, 2008).

Left MTG. When a word is identified and its semantic content accessed, activations diffuse to the left middle temporal cortex (Binder et al., 2009; Hickok and Poeppel, 2004), during passive listening (Jobard et al., 2007) or semantic tasks (Jedidi et al., 2021). At a lesser level, MTG also appears to play a lexical role. During listening to ambiguous stimuli, such as in the "Ganon effect" task (as seen previously, choosing the true word over a pseudoword when listening to this type of stimuli), Bidelman and colleagues (2021) using EEG showed activations in the MTG, supporting this lexical effect.

Left frontal regions. These mainly include the pars opercularis region (Broca's area) and the ventral premotor cortex, and play a role in executive control and working memory. They are involved in sub-lexical language tasks, such as repetition (Price et al., 1996), due to their role in articulatory coding (Burton et al., 2005), or manipulation of phoneme sequences (Démonet et al., 1992). Finally, the left middle and upper frontal regions may play a role in semantic access (Binder et al., 2009), as may the pars triangularis and pars orbitalis, particularly as task difficulty increases (Whitney et al., 2011). The pars opercularis would also play a syntactic role during speech production (Chang et al., 2018) but not in syntax during perception (Rogalsky et al., 2018).

The left fusiform gyrus. Activations of this region during speech listening are reported in the corresponding section *VWFA properties*.

Supplementary and pre-supplementary motor areas. These regions are not classically included in models of language perception, but they are activated by auditory stimuli, whether perceived or imagined. Their role could be the motor representation of perceived sounds, as well as in motor responses to certain stimuli particularly in social interactions (Lima et al., 2016).

Right hemisphere. Although language processing is strongly left lateralized, for some aspects there is right-hemisphere involvement. For example, prosody (Ross and Monnot, 2008), humor, non-verbal language (Johns et al., 2008), and certain voice characteristics (Scott, 2019) are responsible for activation in the right hemisphere.

vi. Synthesis and interactions

When we compare the different networks activated during reading and listening to spoken language, we notice that the regions involved in certain functions are similar. Each of these systems also has its own specificities, whether it's the visual cortex and the VWFA as the gateway to reading, or the primary auditory cortices when listening to spoken language. But we also note that these regions can be activated in the other modality. These findings support the idea of ongoing interactions between the two language modalities, written and spoken.

C. Language models

i. Models of reading

Reading relies on two systems: ventral and dorsal (Cummine et al., 2015; J.S. Taylor et al., 2013). The ventral system is involved in orthographic analysis and word recognition (Ben-Shachar et al., 2011; Vinckier et al., 2007), as well as access to meaning (Carlson et al., 2014). It is based on the occipito-temporal regions described above. The dorsal system is involved in grapheme-phoneme correspondence (Saur et al., 2008; Taylor et al., 2014), enabling the translation of orthographic sequences into phonological ones, and thus reading aloud. It relies on the temporo-parietal regions. The left inferior frontal gyrus is sometimes attached to the anterior part of the dorsal pathway (Schlaggar and McCandliss, 2007), sometimes to the ventral pathway (Oliver et al., 2016).

Ventral pathway: Word identification

While reading, we are able to extract information about the identity of letters from a succession of features combinations, enabling us to identify a word. The identification of this word then gives us access to a set of phonological and lexico-semantic information. Given the different effects reported above, and the types of reading disorders that exist, it is difficult to propose a single model capable of explaining all these effects and disorders, among all those that have been proposed (either attempting to explain the whole of this series of operations or restricting themselves to certain aspects).

→ Most models agree on a hierarchical approach to visual recognition, involving several stages: firstly, **features** recognition, which may lead to the identification of a **letter**, and then

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a **word** by compiling the selected letters (Davis, 2010; Grainger and Jacobs, 1996; McClelland and Rumelhart, 1981; Whitney, 2001). These models also postulate **bidirectional connections** between most levels of processing, each reinforcing or inhibiting the preceding and following levels. The addition of a **degree of uncertainty** following a Gaussian probability distribution in the identification of a word (Grainger and Jacobs, 1996) or letter (Davis, 2010), as well as uncertainty concerning the position of letters in the word (Davis, 2010), helped explain the frequency and density effects of the orthographic neighborhood in lexical decision and perceptual identification. Davis' (2010) model has also been used to explain priming phenomena with letter transposition. Another important notion is that of **open bigrams**, introduced by the **SERIOR** model (Whitney, 2001). This model adds to the previous ones a retinal activation level (by pixels), as well as a bigram level. It states that the letters activated at the bigram level are not necessarily adjacent (e.g. the bigram "CE" would be activated by the word "CHIEN" as well as by the word "PLACE" or "CIEL"), and thus also helps to explain the **flexibility of positional coding**. However, this model fails for words with the same letters several times in a different order, which will have the same coding in open bigrams. The concept of a Gaussian probability distribution for the position of a letter within the word has also been taken up in the **Overlap** model (Gomez et al., 2008), which focuses on the positional coding of letters within the word, in order to explain positional flexibility in the case of transposition, repetition, migration, deletion or insertion of letters.

Despite the various additions and modifications made over the years, some properties have not been integrated into these models. These include case invariance (an "A" and an "a" are recognized in the same way) and location invariance (the word "dog" can be read in the same way at different locations in the visual field). In 1987, Mozer incorporated location invariance into his model, but not case invariance.

Local Combination Detector model

→ Only the **Local Combination Detector** (LCD; Dehaene et al., 2005) model manages to integrate these different parameters. This model states that the left ventral occipitotemporal cortex (vOTC) is organized into several modules along a posterior-anterior gradient, terminating at the VWFA (**Figure 1.3**).

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Following this gradient, the modules are of increasing sensitivity to stimuli of increasing orthographic complexity: **physical features**, then **letters**, **bigrams**, **quadrigrams** and finally **words**. This increase in the complexity of the information processed is accompanied by a **progressive widening of the neuron's receptive fields**, since at each level, the neuron synthesizes information from several previous-level neurons, which themselves have a smaller receptive field.

- The first level of processing therefore takes place in the most posterior regions of the occipital cortex, and corresponds to physical **features** recognition (bars, contours, angles).

- At the next, more anterior level, information concerning these strokes converges on a shape detector neuron, which will be able to recognize a **letter**, in a certain case and typography only. For example, when presented with an "A", a first neuron recognizing the stroke combinations forming an "A" is activated, while another neuron, activated only by the stroke combinations of an "a", is not.

- At a higher level, a 3rd neuron, activated for the **abstract identity of the letter A** (i.e., disregarding its visual representation), independently of case or typography, synthesizes the information coming from these two neurons, enabling it to identify the abstract identity of the letter A.

- In the next stage, still following a posterior-anterior gradient, the activated neurons synthesize the **local combinations of letters** from the previous level. For example, a given neuron is activated by the presence of a "C" to the left of an "I", even in the presence of one or two letters in between. This neuron will be able to recognize this sequence at **different spatial locations**, as it receives information from different neurons detecting the "C" or "I", each in different receptive fields. This gradual broadening of the receptive field could also explain how **open bigrams** work, as introduced by Whitney (2001): inaccuracy in letter localization results from the fact that the bigram detector receives information from multiple neurons, and therefore multiple receptive fields. However, this invariance to localization is limited to a certain area for a bigram detector. A multitude of detectors of a given bigram are therefore needed, to cover a wider visual field. Consequently, in a word containing the same letters several times, the same detectors will not be activated when the same combination of letters is presented at different positions in the word (a phenomenon not resolved in

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Whitney's model). This model also considers frequency effects, since less frequently encountered bigrams will be less and less represented on the scale of bigram detectors.

Figure 1.3

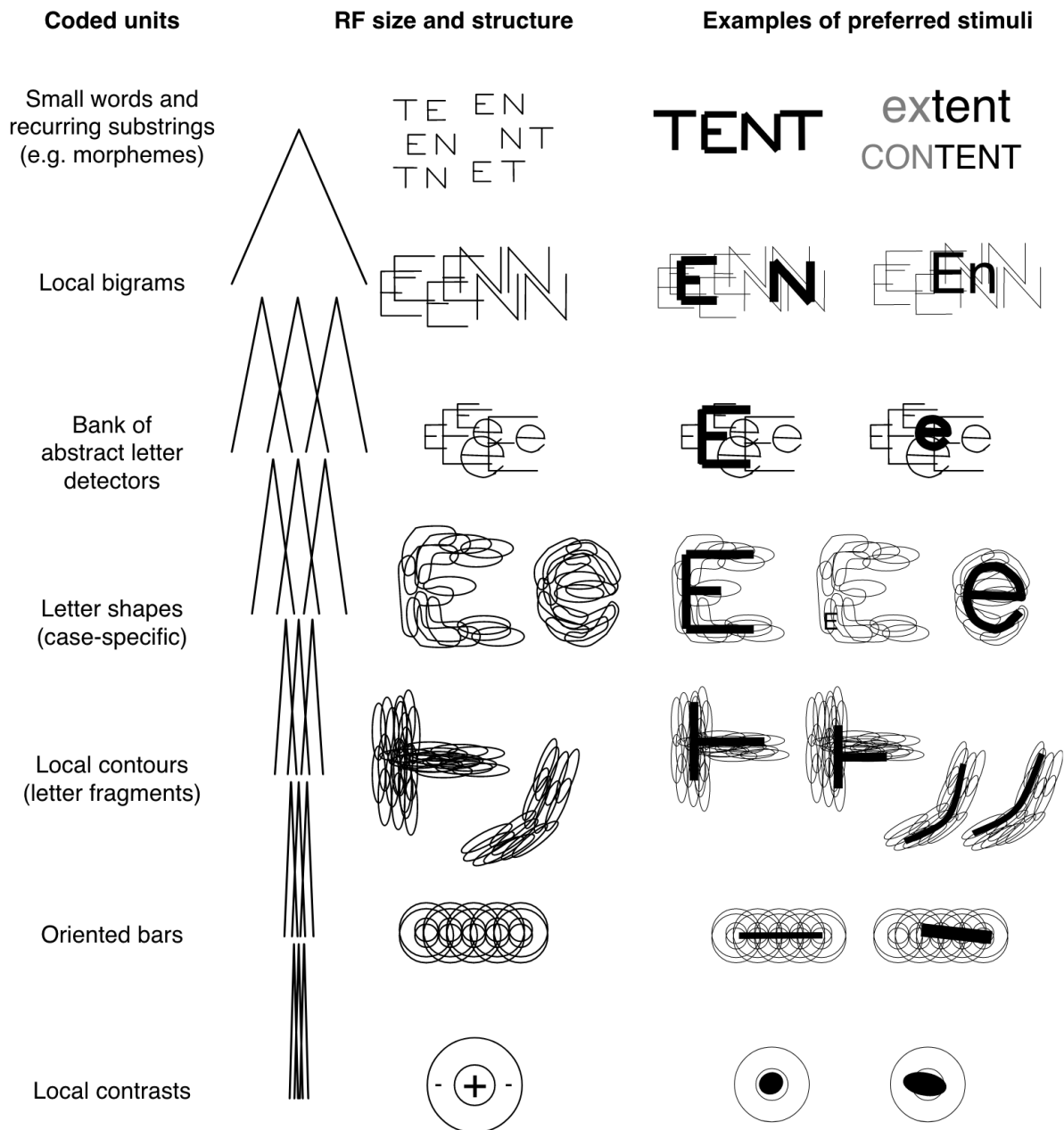


Figure 1.3. Model of the local combination detector. Each neuron pools activity from a subset of neurons at the immediately lower level, leading to an increasing complexity, invariance and size of the receptive field at each stage.

Adapted from Dehaene et al. 2005.

Finally, it is the only model that attempts to propose **anatomical substrates** at the various stages of treatment.

The previously cited work by Dehaene et al. (2004), on the influence of letter order and position, also supports a non-uniform organization of the vOTC. Indeed, they identify 2 subregions with different activation properties within the VWFA: the most anterior recognizes a word and its circular anagram in the same way and may therefore be composed of bigram detectors; the most posterior recognizes the same letter in a specific location in the same way, and may therefore be composed of location-specific letter detectors.

Later Vinckier et al., (2007), presented participants with visual stimuli of various kinds, and with orthographic complexity progressively approaching that of a word: chains of pseudo-letters, chains of rare then frequent letters forming rare bigrams, frequent bigrams, frequent quadrigrams, and real words. On functional MRI, they showed that activation in the fusiform gyrus became increasingly specific for real words, following a **continuous** (rather than discrete) **posterior-anterior gradient** (see **Figure 1.4**), echoing the bigram frequency-sensitivity effect highlighted by Binder et al. (2006).

Lerma-Usabiaga et al. (2018) also showed a two-part organization of the left vOTC, with an anterior module more sensitive to lexical contrasts (words > pseudowords), and a posterior module more sensitive to sub-lexical components (notably orthographic, with a word > checkerboard contrast for example).

Finally, more recent work (Zhan et al., 2023) has also found increasing sensitivity to orthographic similarity with a word, along the same posterior-anterior gradient as Vinckier et al. (2007), results again compatible with the LCD model.

Figure 1.4

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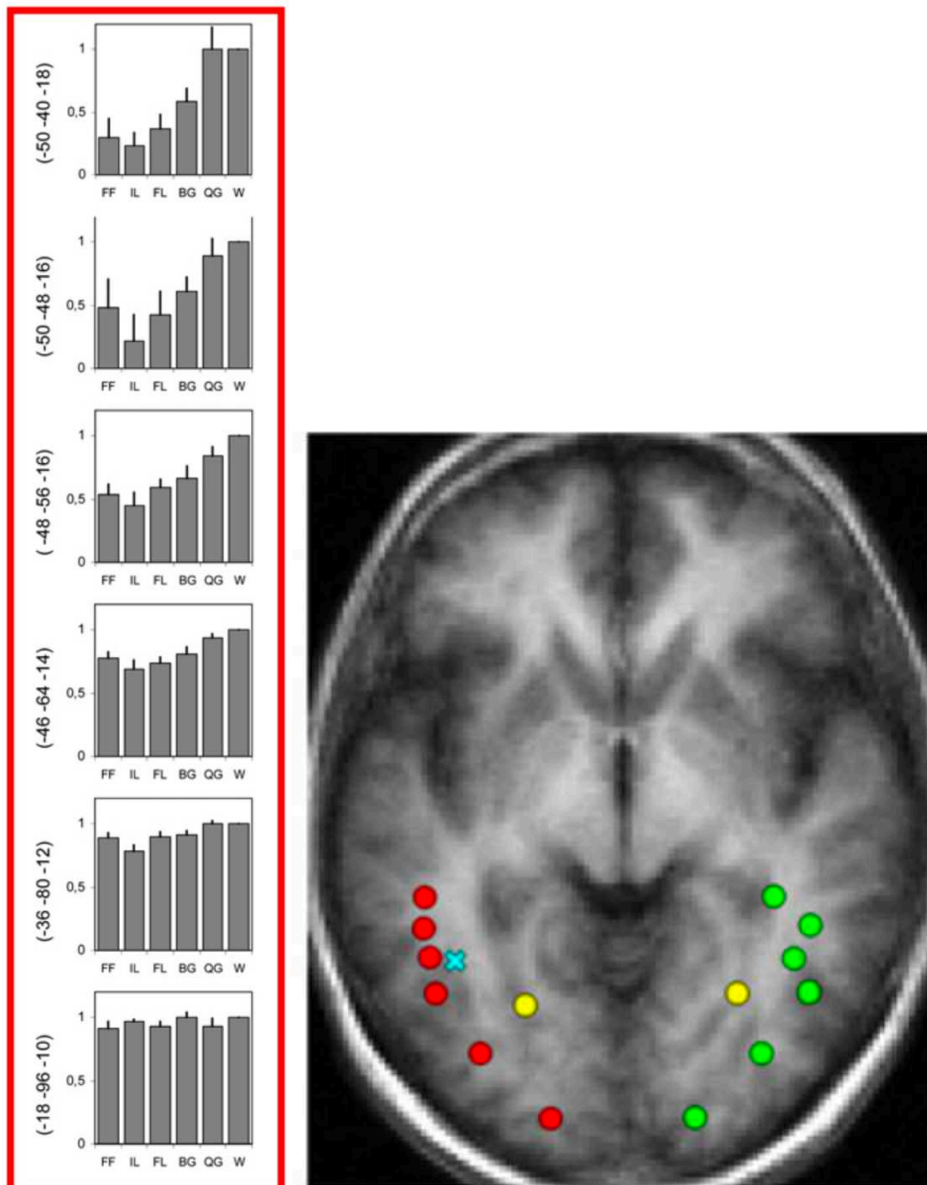


Figure 1.4. Activation in the left ventral occipitotemporal cortex for different categories of orthographic stimuli. Regions in red on the right-hand side of the figure correspond to the different coordinates shown on the left-hand side of the diagrams. The most posterior regions activate with the same intensity for all categories, while anteriorly, quadrigrams and real words are responsible for greater activation.

FF = False fonts, IL = Infrequent letters, FL = Frequent letters, BG = Frequent bigrams, QG = Frequent quadrigrams, W = Words.

Adapted from Vinckier et al., 2007.

Taken together, these results support a **modular organization** of vOTC, with increasing preferential activation for word-like stimuli along a posterior-anterior gradient.

Top-Down influences

The LCD model only takes into account potential feed-forward, bottom-up connections within the VWFA, whereas we know that there are also top-down connections, influencing the system in a retrograde manner.

Ventral propagation along an anterior-posterior gradient. For example, this model does not explain word frequency effects, nor word superiority effects over a pseudoword. Recently, Woolnough et al. (2020) recorded intracranial electrical activity in the ventral cortex of epileptic patients, and confirmed some of the postulates of the LCD model. In particular, they found that orthographic sensitivity is prioritized along a posterior-anterior gradient. However, this work also provides new information. They show that a region anterior to the VWFA (MNI $Y > -40$) is the first to distinguish a word from a non-word, as well as to process the lexical frequency of the word. These effects then propagate along an anterior-posterior gradient towards the VWFA. This suggests bidirectional connections between the different stages of visual processing at the level of the left vOTC, as stipulated in the various models previously presented (Grainger and Jacobs, 1996; McClelland and Rumelhart, 1981; Whitney, 2001), but not specified in the LCD. These studies also suggest that the lexical effects observed in the VWFA are more related to top-down effects.

Absence of vOTc specialization? More radically, Price and Devlin (2011) consider that there is no local specialization of left vOTC neurons for orthographic stimuli, but that all the effects observed are merely the reflection of top-down connections, originating from higher, semantic and phonological regions, without however specifying the anatomical regions possibly involved. Other works previously detailed, also report activations of the VWFA during Braille reading (Kim et al., 2017), or during language listening (Dehaene et al., 2010b; Yoncheva et al., 2010), also suggesting activations of the VWFA by higher regions. It is likely that these remote regions play a role in certain lexical aspects of word recognition.

VWFA connectivity. The remote regions mentioned above could be language regions, given the activations of the VWFA during tasks involving language without visual stimulation, and given the various structural connectivity studies. The most anterior parts of the left vOTc could

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be connected to the left supramarginal and angular gyri via the posterior portion of the arcuate fasciculus, and to the left inferior frontal regions via the long portion of the same fasciculus (Lerma-Usabiaga et al., 2018). Other studies have also shown that there is significant structural connectivity between the VWFA and the supramarginal gyrus (Epelbaum et al., 2008), even more so when phonological demand is greater (Florence Bouhali et al., 2019). More generally, the VWFA has also been shown to be more strongly connected to language and attention regions (Chen et al., 2019). There are also privileged connections at rest in functional MRI between the VWFA and language regions, in adults (Stevens et al., 2017) but also in children, pre-literacy (Li et al., 2020), conditioning its future location.

The dual route model

These steps are sufficient in most cases, but it is sometimes necessary to transform a written sequence into a phonological one: when we want to **read aloud**, or more rarely, when a word is not in our lexical stock. The main model that has been proposed is the **Dual Route Cascaded model** (Coltheart et al., 2001). This model includes a lexical route and a sub-lexical route. Once the letters have been identified upstream, they are processed serially from left to right. In the **lexical route**, letters activate word units in the orthographic lexicon, which in turn activate units in the phonological lexicon. This in turn activates the corresponding output phonemes. In the **sub-lexical route**, each letter or group of letters is associated with the corresponding output phoneme via grapheme-phoneme conversion rules. In both cases, the phonemic output is then stored and assembled in the phonologic output buffer. These two routes are processed in parallel, so the phonological output sequence depends on both. When words have a high lexical frequency, lexical orthographic and then phonological access is faster than processing via the sub-lexical route, so phonemic output depends solely on the lexical route, including for irregular words. On the other hand, for a low-frequency word, the sub-lexical route is faster, so phonological errors may occur in the case of irregular words. The position effect of the irregularity also favors serial letter processing in this model: when the irregularity is at the end of the word, the lexical route will have identified the word before the irregularity is processed by the sub-lexical route, whereas there is likely to be conflict between the two routes when the irregularity occurs early in the word. Finally, pseudowords are only processed by the sub-lexical route.

Other parameters

Finally, there are also other models focusing primarily on other parameters, such as oculomotor control during reading, in order to understand eye movements during the reading of sentences and texts (Engbert et al., 2002; Pollatsek et al., 2006; Reichle et al., 2009). However, some authors have tried to integrate a visual-attentional parameter into their models, such as the **MultiTrace Memory model** (Ans et al., 1998), which focuses on the phonological transformation of written sequences.

In summary

Overall, none of the proposed models is sufficient on its own to explain all the effects observed in behavioral tests or functional MRI tasks. According to some models, the word identification process relies solely on local properties, linked to a specialization of the ventral cortex for reading with the learning of reading (Dehaene et al., 2005), with an exclusively bottom-up progression of information. Others, on the contrary, suggest that this region acquires no specialization when learning to read, and that all the effects observed are linked to top-down effects, with no specialization of the ventral cortex for orthographic stimuli (Price and Devlin, 2011). Finally, most models stipulate bi-directional interactions to explain the processing of visual information (Davis, 2010; Grainger and Jacobs, 1996; McClelland and Rumelhart, 1981; Whitney, 2001). By considering the mechanisms involved in reading aloud, we add a level of variability to the model.

→ It can be assumed that these models are complementary, and each explains certain aspects of reading. Firstly, there is bottom-up processing of visual aspects in the left vOTC, along a posterior-anterior gradient, transforming strokes into letters, bigrams and words. In addition, more abstract aspects such as stimulus lexicality, or word frequency, could be processed in a more anterior region of the left vOTC (Woolnough et al., 2020), and would probably result from top-down effects from regions more or less at a distance, which could correspond to language regions (Lerma-Usabiaga et al., 2018). Next, the production of a phonological version of this word will depend on its identification: if it is identified, the various phonological and semantic information concerning it is accessed via the lexical pathway; otherwise, a grapheme-phoneme transposition is performed via the sub-lexical pathway.

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ii. Speech models

Dual stream model

The main accepted model of concurrent is the dual stream model (Hickok and Poeppel, 2015, 2007, 2004). In their model, Hickok and Poeppel specify a ventral and a dorsal pathway (**Figure 1.5**).

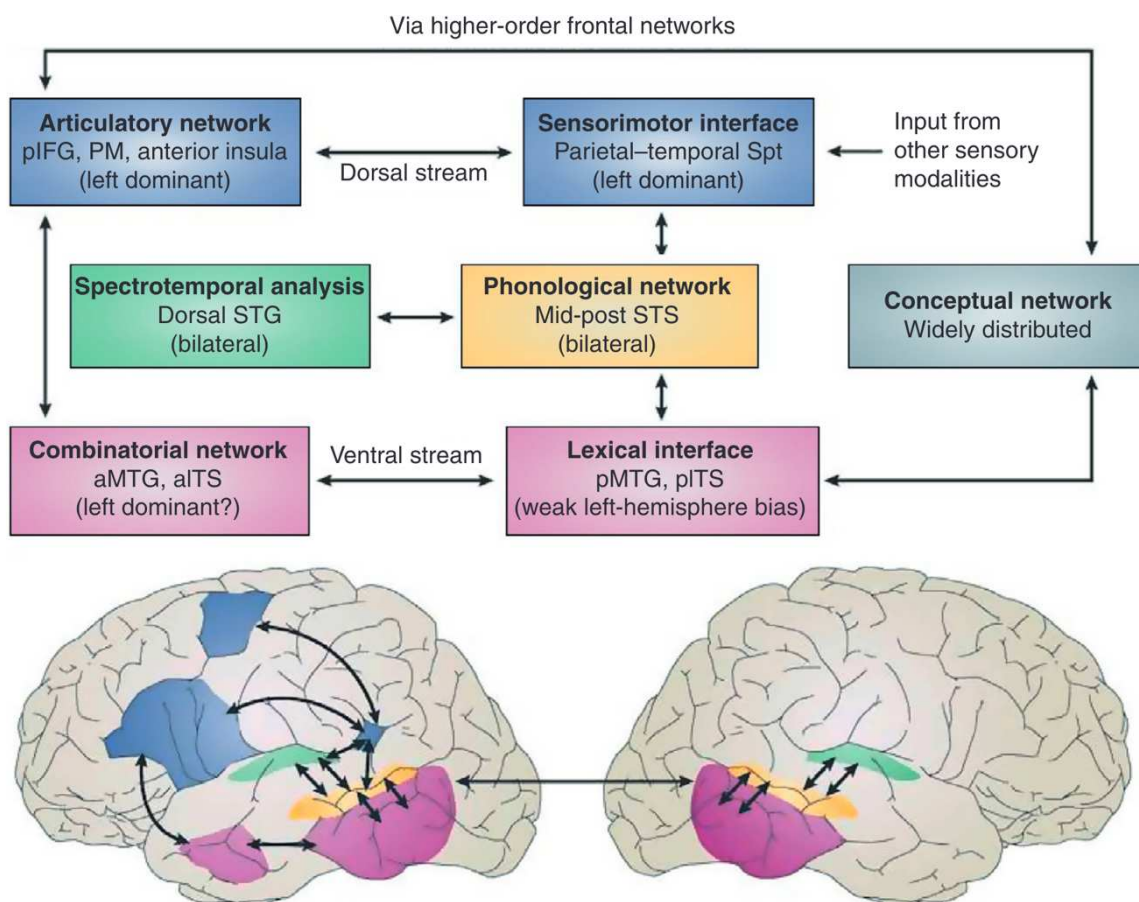
Common pathway. The first part of speech processing is common, and consists in analyzing the sounds heard to extract the **phonology**. It begins at the level of the **bilateral STG**, with the perception of language and non-language sounds. According to some authors, the processing of **intelligible** sounds will tend to be left lateralized within the STS (Narain, 2003; Scott, 2000), while others suggest bilateral processing of intelligible sounds (Okada et al., 2010; C.J. Price, 2012). In fact, both hemispheres could be involved in processing different acoustic aspects of the sounds heard (Obleser et al., 2008). **Phonological** processing then takes place in the STS. It is not clear whether this processing takes place in the anterior or posterior portion of the STS. Studies showing that activation is more anterior (Scott, 2000; Spitsyna et al., 2006) used sentence stimuli, so anterior activation could reflect syntactic processing.

The ventral pathway. Its role is to extract the meaning of words from phonological sequences. Semantic information is stored diffusely at cortical level, according to the model, while the ventral pathway represents the interface between phonological and semantic information. The operation that establishes the correspondence between these two types of information would take place in the bilateral, left-predominant **MTG** (Binder et al., 2009; Davey et al., 2016; Lau et al., 2008). The hypothesis of the role of the anterior temporal regions comes mainly from imaging analyses of patients with primary progressive semantic aphasia, but who have other regions also involved, so asserting the role of these anterior regions in semantic processing is challenging. Rather, their role is syntactic, structuring and combining elements (Brennan and Pykkänen, 2012; Pallier et al., 2011).

The dorsal pathway. Initially thought to play a role in auditory spatial localization ("where" pathway; Rauschecker, 1998), it ultimately has a role in sensory-motor integration. The links between the sensory and motor sides of a domain are crucial. Indeed, a motor action (be it the movement of a hand or the contraction of the vocal cords) is aimed at a precise goal and needs live feedback to adjust the continuation of the motor action to progress in relation to

the goal. Conversely, our sensory system needs to be notified of our motor actions, at the risk of feeling that the world is moving and becoming dizzy when we turn our head (Haarmeier et al., 1997; Shadmehr et al., 2010). During concurrent perception, this sensory-motor integration is not essential for comprehension, but it is during language production (Purcell and Munhall, 2006). The role of this dorsal pathway would be to establish the correspondence between the perceived phonological sequence, and the sequence of motor patterns enabling reproduction of this sequence. This integration would take place at the level of the **left sylvian parieto-temporal junction** (Spt) in the Planum Temporale (Hickok et al., 2003; Pa and Hickok, 2008), whose activity would be strongly correlated with that of the pars opercularis (Buchsbaum et al., 2005b, 2001), which would have a production role. A lesion of the Spt would mainly disrupt the ability to correct concurrent production, resulting in a picture of conduction aphasia.

Figure 1.5



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Figure 1.5. Two-way model. Sounds are first perceived in the bilateral STGs (green), then phonological analysis takes place in the posterior regions of the STSs (yellow). Two pathways are then distinguished: the ventral pathway (pink), providing access to lexical-semantic information, and the dorsal pathway (blue), enabling sensory-motor integration. Semantic information, stored diffusely in the cortex, is shown in gray.

Adapted from Hickok and Poeppel (2015).

D. Categorical organization of the visual cortex

Orthographic stimuli are not the only ones to have a dedicated area of visual cortex. This is also the case for other types of visual stimuli (**Figure 1.6**). For example, there is the Fusiform Face Area (FFA) in the right fusiform gyrus, symmetrical to the VWFA, and the Occipital Face Area (OFA), which is specialized for face recognition (Kanwisher et al., 1997; Puce et al., 1996). Another region, in the bilateral parahippocampus, is specialized in visual place processing, the Para-hippocampal Place Area (PPA; Epstein and Kanwisher, 1998). There are also specialized areas for body parts, with the Extrastriate Body Area (EBA; Downing et al., 2001) in the right lateral occipitotemporal, and the Fusiform Body Area (Peelen and Downing, 2005) in the right fusiform gyrus. Finally, there's the Lateral Occipital Complex (LOC), in the bilateral latero-ventral occipital cortex, specialized in object and tool recognition (Grill-Spector et al., 1999).

Figure 1.6

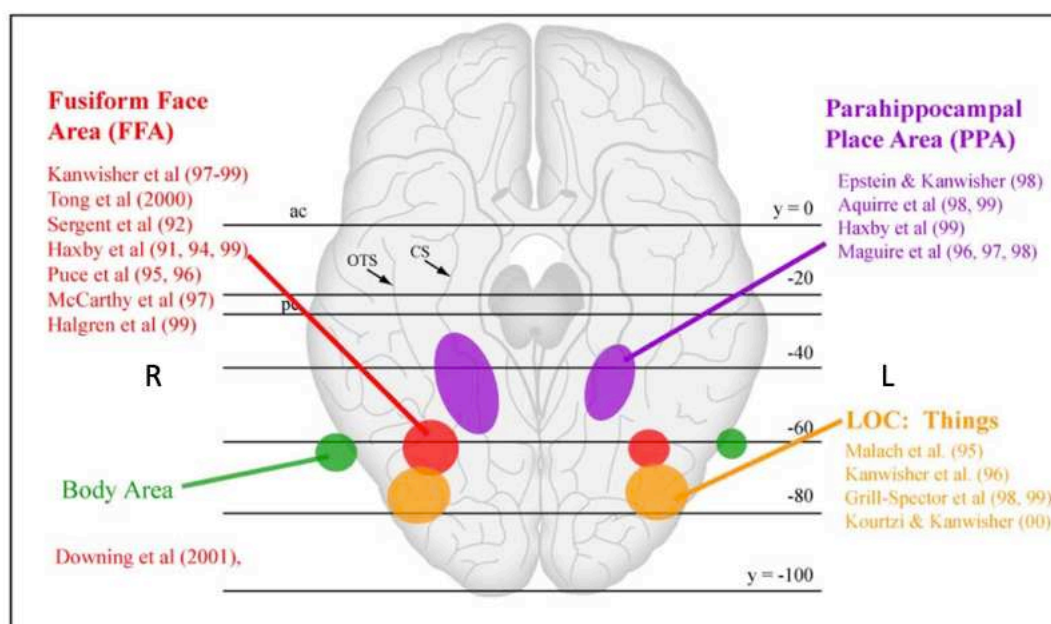


Figure 1.6. View of the bilateral ventral occipito-temporal cortex (right hemisphere on the left), showing the different area specialized for faces, places, bodies and objects.

Figure by MIT OpenCourseWare 2007.

2. Reading disorders

The models described above attempt to take account of possible dysfunctions in language, both written and spoken, and have been improved, refined, or even created in an attempt to explain them. We distinguish between developmental and acquired disorders, which may affect language, reading or both. This work does not focus specifically on reading under pathological conditions, but the study of developmental disorders also makes it possible to target a set of regions that may be involved in certain specific stages identified as dysfunctional. The study of acquired reading disorders, for its part, remains an interesting method of study compared with imaging healthy subjects, as it enables us to demonstrate the causal involvement and necessary role of a region in a given cognitive process.

A. Developmental disorder: dyslexia

i. Definition

Developmental dyslexia is characterized by difficulties in word recognition, in the absence of cognitive or sensory deficits, despite adapted instructions (Lyon et al., 2003). It is one of the most common neurodevelopmental disorders, with a prevalence that varies according to the thresholds chosen, estimated at between 3% and 12% (Fletcher et al., 2018; Katusic et al., 2001), generally below 10% (Hoeft et al., 2015). This variability according to the thresholds chosen can be explained by the fact that the diagnostic parameters measured are distributed along a continuum in the population (Fletcher et al., 2018). Dyslexia is not a transient disorder during childhood, there is persistence of disorders into adolescence (Shaywitz et al., 1999), and there is no remission or catch-up of dyslexia-related difficulties. Finally, there are no comprehension difficulties in the strict sense; it's the identification of perceived orthographic stimuli that is problematic, even if comprehension may be impaired by the high attentional cost of identification difficulties. The dysfunction may occur at different stages of the visual identification process, or in grapheme-phoneme conversion, resulting in different types of

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dyslexia. The treatment of dyslexia relies on precise identification of the level of dysfunction, so that speech therapy can be adapted as far as possible.

ii. Classification

Since 1965 (Myklebust), it has been known that there are several forms of dyslexia. Initially, Myklebust distinguished between auditory dyslexia, where it was difficult for the patient to associate sounds with letters, and visual dyslexia, where it was difficult to visualize letters mentally. Since then, studies on the subject have multiplied, and classification has become more complex as it has been refined. One of the current classifications (Friedmann and Coltheart, 2018) is based on the dual route model (Coltheart et al., 2001, see **Figure 1.7**).

Peripheral dyslexia

In the dual route model, the first stage of visual orthographic analysis comprises three steps: abstract letter identification (e.g., recognizing that a character represents an "A"); the position of a letter within a word; and associating letters to form a word. A lesion in one of these stages will cause different types of reading disorders, grouped together under the term peripheral dyslexia.

Letter identity dyslexia. People with this type of dyslexia have difficulty recognizing and naming a letter (Brunsdon et al., 2006), especially visually close graphemes such as "b" and "d" or "m" and "n". They are also unable to match an uppercase letter with its lowercase equivalent. This makes it difficult to identify individual letters and may result in omissions or substitutions of letters in certain words.

Letter position dyslexia. Letter position dyslexia (e.g., "CHIEN" and "CHINE"). This type of dyslexia has already been reported in English (Kezilas et al., 2014), Hebrew (Friedmann et al., 2015), Arabic, Italian, etc. There may be omissions of a letter when it occurs twice in a word, since the 2 copies of the same letter in a given word differ only in their position within the word, which the person cannot encode. The semantic context of a sentence can reduce dyslexia-related discomfort (Friedmann and Rahamim, 2007).

Attentional dyslexia. In attentional dyslexia, letters migrate between neighboring words (e.g. in French, "la mouche bouge" et "la bouche bouge"). This dyslexia is not linked to an attentional disorder, contrary to what its name suggests. The relative position of a letter

within a word is generally preserved. The letter may migrate between two vertically adjacent words (from one line to another). This dyslexia has also been described in several languages (English: Friedmann et al., 2010; Arabic: Friedmann and Haddad-Hanna, 2014; Italian, etc). In this dyslexia, it's possible for the same letter appearing in the same position in two neighboring words to be omitted: the letter being identical in its abstract identity and position in the word, it differs only in that it belongs to a different word, so the person doesn't realize that there are twice that letter.

Figure 1.7

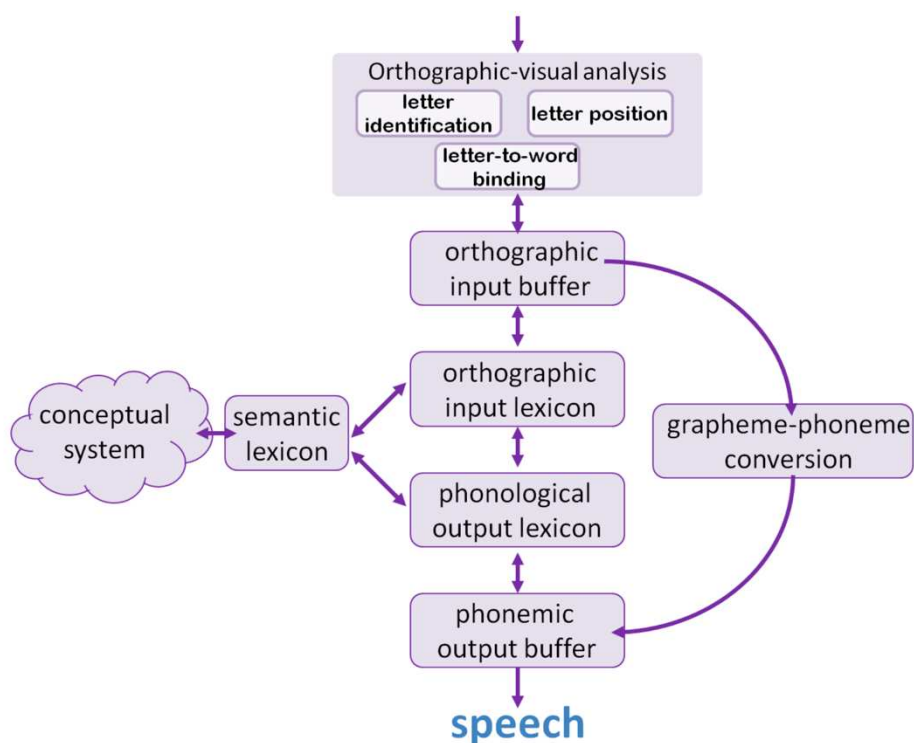


Figure 1.7. Representation of the two-way model according to Coltheart et al., 2001. The first step in word processing is the orthographic analysis. The outgoing information is then transferred to the orthographic buffer, which acts as a working memory, and identifies the word morpheme. Stimuli are parallelly processed in the lexical and sub-lexical routes. For real words, the orthographic lexicon can access the word's semantic information, enabling it to be identified in the phonological lexicon. The phonological lexicon also provides parallel access to the corresponding phonological information. This is the lexical route. Non-real words or unknown words takes the sub-lexical route, based on grapheme-phoneme conversion. The

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final stage common to these two routes is the phonological output buffer, which stores phonological information in working memory, assembles it and enables oral production.

Adapted from Friedmann and Coltheart, 2018.

Neglect dyslexia. This dyslexia is usually described in its acquired form (for review, see Vallar et al., 2010), but can also be developmental at the word level. Affected individuals will neglect the left (most commonly; Friedmann and Coltheart, 2018) or right part of a word (e.g. reading "mais" instead of "maison" or "parfait" instead of "imparfait"). In addition to these omissions, there may also be letter additions or substitutions, particularly when this results in an existing word. In its developmental form, it is described with neglect of the left part of the word when the language is read from right to left, such as Hebrew (Friedmann and Nachman-Katz, 2004) or Arabic (Friedmann and Haddad-Hanna, 2014).

Visual dyslexia. This is the consequence of a deficit in the output of visual orthographic analysis (Marshall and Newcombe, 1973) and therefore affects all the stages previously mentioned. Errors may therefore concern the identity of letters, and there may also be substitutions between words or within a word. According to Marshall and Newcombe, there are subtypes of visual dyslexia, corresponding to the nature of the visual impairment. These subtypes correspond to the previous types of dyslexia (letter identity, letter position and attentional).

Central dyslexia

Central dyslexias are linked to anomalies after the orthographic analysis stage. They may affect the lexical or sub-lexical route.

Surface dyslexia. This is linked to a deficit in the lexical route (Coltheart et al., 1983). Reading is therefore mainly mediated by the sub-lexical route, and the main difficulty concerns the pronunciation of irregular words (such as "oignon" or "yacht"). Access to the word's lexical-semantic information, and therefore its comprehension, can also be disrupted when the orthographic lexicon is affected. The sub-lexical pathway can provide access to word meaning via the phonological lexicon. Phonological production is monitored, and people with surface dyslexia generally try to compensate by producing only words they know. This compensation is difficult, however, for homophones (e.g. "mer" and "maire") or "potentiophones", which

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are the result of grapheme-phoneme conversion according to standard rules, without taking irregularities into account, thus resulting in an excess of regularization (e.g. "clown" and "clone"). Pseudoword reading, on the other hand, is preserved by the sub-lexical pathway. There are different types of surface dyslexia, depending on the degree of impairment in the lexical pathway: if the *orthographic lexicon* is affected, reading aloud, lexical decision making on pseudo-homophones (e.g. whether "lontan" is a real word) and homophone comprehension are impaired; if the *connections between the orthographic lexicon and the semantic and phonological lexicon* are affected, lexical decision making is not impaired, but homophone comprehension is; if only the *connection between the orthographic lexicon and the phonological lexicon* is affected, only reading aloud is disrupted, while lexical decision making and homophone comprehension are not; finally, if the *phonological lexicon* is affected, concurrent production is disrupted, whether in naming tasks or spontaneous speech.

Phonological dyslexia. In this case, the sub-lexical pathway is affected, so reading is only possible via the lexical pathway (Coltheart, 1996). The reading of pseudowords and new words is impaired. Impairment of the sub-lexical pathway can occur at different levels. There may be an abnormality in the conversion of an isolated letter into a phoneme, thus disrupting even the reading of isolated letters. Conversion disorders may also involve one or more letters, depending on the context in which they are presented (for example, the pronunciation of the letters "ch" varies according to the presentation in the word "écharpe" or "orchestre"; Marshall and Newcombe, 1973). The impairment may also be at the level of the phonological buffer, where the assembly of different phonological sequences takes place. In this case, reading isolated letters is not a problem. Pseudowords are predominantly affected, as word pronunciation is supported by the phonological lexicon, but the reading of morphologically complex words may be impaired. There is a length effect when reading aloud words and pseudowords, with omissions, substitutions, and transpositions of phonemes. In people with this dyslexia, there may also be difficulties outside reading, i.e. when repeating or producing concurrent (Dotan and Friedmann, 2015).

Vowel dyslexia. This is an impairment of the sub-lexical pathway that specifically affects vowels (Khentov-Kraus and Friedmann, 2011). These difficulties relate solely to pseudowords and new words. Problems occur more often when the vowel error results in an existing word.

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Profound dyslexia. This is characterized by semantic errors during reading (Stuart and Howard, 1995). There may also be morphological errors (e.g., "singers" read "song"). This phenotype could be linked to dysfunctions in the sub-lexical pathway, as well as in the lexical pathway between the orthographic lexicon and the phonological lexicon. The reader is therefore forced to read via semantic access (e.g., "jovial" can be read as "joie"). Pseudoword reading is very difficult, as the person tries to lexicalize the stimulus (e.g., "fien" read "chien"), otherwise they are unable to read it. Morphologically complex words are also difficult to read, with omissions and substitutions. Syntactic difficulties may also be present (Friedmann and Coltheart, 2018).

Semantic access dyslexia. People with this dyslexia have no difficulty reading aloud, whether real words or pseudowords, but cannot understand their meaning (Castles et al., 2010). The impairment is thought to lie in the connection between the orthographic lexicon and the semantic lexicon.

iii. Origin

There are many causes of developmental dyslexia, some of which are related to influences on learning to read.

Genetic

The main cause is genetic, with moderate heritability (Pennington and Olson, 2005). A number of twin studies at different ages have also shown a link between genetics and dyslexia (Harlaar et al., 2005b; Light and DeFries, 1995). With the emergence and democratization of new genomic analysis techniques, various studies have identified up to 42 loci involved in dyslexia (Doust et al., 2022; Fisher and DeFries, 2002; McGrath et al., 2006) and a number of genes have been identified (Gialluisi et al., 2021; Kere, 2011), which might be involved in neuronal migration or axon guidance, for example.

Environment

Among the factors predisposing to dyslexia, the genetic component accounts for up to 70-80% (Schumacher et al., 2007). There are, however, environmental factors influencing reading development. For example, stress (Theodoridou et al., 2021) or a lower socio-economic level (Zuk et al., 2021) may favor the development of reading disorders. Other factors as good oral-

language skills (Carroll et al., 2014; Hulme et al., 2015), or early language abilities such as vocabulary knowledge (Snowling and Melby-Lervåg, 2016) may be protective, even in non-at-risk children. Increased attention skills, memory and general intelligence have also been reported as protective in at-risk children (Haft et al., 2016). In non-at-risk children, the socioeconomic status (Fernald et al., 2013) and the literacy environment after controlling for socioeconomic status (Van Steensel, 2006) were also reported as protective factors.. Finally, language transparency is also a factor in the onset of dyslexia, with highly transparent languages such as Spanish associated with a lower prevalence of dyslexia than other less transparent languages such as English (for review, see Borleffs et al., 2019). Note that there is an interaction between environmental factors and genetics: using parents' average educational level as a reflection of their socio-economic level and other environmental factors, Friend et al. (2008) showed that genetic influence was stronger and environmental influence weaker when parents' socio-educational level was stronger (Friend et al., 2008).

iv. Anatomical correlates

A number of regions have been reported to be involved in dyslexia, both in terms of functional activation and anatomical measures. A number of meta-analyses have focused on regions of the left hemisphere that are also involved in reading (Linkersdörfer et al., 2012; Maisog et al., 2008; Paulesu et al., 2014; Richlan et al., 2011, 2009). These regions are organized into two sets, a dorsal temporo-parietal consisting of the inferior parietal lobule, SMG, STG, and a ventral including the fusiform gyrus. The left inferior frontal gyrus is also present.

Temporoparietal regions. The posterior pathway is involved in grapheme-phoneme correspondence during reading. In their meta-analysis, Linkersdörfer and colleagues (2012) reviewed 9 morphometric studies of people with dyslexia and 24 functional MRI studies. They identified a decrease in gray matter density in these temporo-parietal regions, particularly the in the SMG. Temporo-parietal regions are also less activated on functional MRI during phonological tasks (Maisog et al., 2008; Temple et al., 2001), even at the same reading level (Hoeft et al., 2007). However, when reading and concurrent performance improved following rehabilitation, activation in this region partially normalized (Temple et al., 2003). In another meta-analysis, Richlan and colleagues (2011) also report under-activations of the left superior temporal gyrus only in adult dyslexics. Finally, Raschle and colleagues (2011) showed that these gray matter differences were present in children with familial dyslexia prior to learning

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to read, suggesting that these differences were a cause rather than a consequence of reading difficulties.

Occipitotemporal regions. The ventral pathway is involved in orthographic character recognition. In the meta-analysis by Linkersdörfer and colleagues (2012), the authors also identify a decrease in gray matter density in the left fusiform gyrus region (Kronbichler et al., 2008). As with the temporo-parietal regions, Raschle and colleagues (2011) also found gray matter abnormalities in this region prior to learning to read, suggesting that these abnormalities represent the cause rather than the consequence of reading difficulties. During various reading tasks on functional MRI, the left occipitotemporal cortex is less activated in dyslexic individuals (Kronbichler et al., 2006; Maisog et al., 2008), in childhood or adulthood (Pugh et al., 2001). Richlan and colleagues (2011) report a decrease in activation on functional MRI in this region mainly in adults, whereas in children, the under-activated cluster represents a more anterior portion of the left vOTC. This age-related difference could in fact be linked to paradigm differences between adult and pediatric studies. Finally, another prospective study in children with familial dyslexia (Maurer et al., 2007), using EEG, showed slower and less left vOTC specialization for words in dyslexic children. Taken together, these findings support an early role for occipitotemporal regions in dyslexia. Finally, in their meta-analysis, Linkersdörfer and colleagues (2012) report significant overlap between the anatomical and functional regions identified, with each possibly secondary to the other.

Left inferior frontal gyrus. There appears to be no morphometric difference between dyslexics and non-dyslexics, although some studies have shown asymmetry between left and right inferior frontal regions (Robichon et al., 2000). Only Brown et al. (2001) report a decrease in gray matter density in the left inferior frontal gyrus in dyslexics. Gray matter density in this region appears to be correlated with performance on tasks involving phonological processing (Pernet et al., 2009; Vinckenbosch et al., 2005). Abnormalities in this region are thought to be a consequence of reading difficulties.

Connectivity. People with dyslexia also have abnormalities in connectivity, with Paulesu (1996) even describing dyslexia as a "disconnection syndrome". In particular, there is a decrease in fractional anisotropy (FA) in certain white matter tracts involved in reading, such as the arcuate fasciculus (Vanderauwera et al., 2017; Maaïke Vandermosten et al., 2012a, 2012b; Žarić et al., 2018), which connects Broca's and Wernicke's regions. More recently,

other studies have shown anomalies in the vertical occipital fasciculus, connecting the left vOTC to the lateral occipital and inferior parietal regions (Sihvonen et al., 2021), or in the left inferior occipito-frontal fasciculus, connecting the left vOTC to the inferior frontal regions (Vanderauwera et al., 2017; Vandermosten et al., 2015). Graph-theoretic analyses have also shown regional network abnormalities in inferior frontal and left temporo-parietal regions in children with familial dyslexia (Hosseini et al., 2013), as well as connectivity abnormalities between occipito-temporal and left temporo-parietal regions (Lou et al., 2019). Functional connectivity is also disrupted. At the level of visual networks, with decreased synchronization within the occipitotemporal cortex, particularly the VWFA (Finn et al., 2014), as well as different resting patterns of functional connectivity between children with and without familial dyslexia (Yu et al., 2022). Van Der Mark and colleagues (2011) showed differences in functional connectivity during a reading task from the VWFA to other language regions in dyslexic children.

In summary, dyslexia, the main developmental reading disorder, manifests itself in different forms depending on the level of impairment. Imaging and electrophysiological studies have shown the involvement of two phenomena. On the one hand, there are structural and functional abnormalities in the temporo-parietal and occipitotemporal regions involved in reading networks. Secondly, there are structural and functional connectivity anomalies between these regions. All these studies show abnormalities in the ventral and dorsal pathways of the reading network, but it is not yet clear which effects are causal and which are secondary to reading difficulties.

B. Acquired disorders

Language disorders of vascular origin. The location and nature of lesions can vary enormously. They may be inflammatory, tumoral or vascular. The lesions most frequently studied in neuropsychology are vascular lesions because their onset is sudden, and it is usually in the context of vascular damage that symptoms are most often isolated. Stroke is one of the most frequent causes of morbidity and mortality (Donkor, 2018), and language disorders are present in around a third of cases (Pedersen et al., 2004). The symptomatology resulting from

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such lesions is similarly varied and, depending on the location of the lesion, may result in isolated impairment of oral or written language, comprehension or expression, repetition, or combinations of these (for review, see Dronkers et al., 2004; Sinanović et al., 2011). For the sake of clarity and conciseness, we will primarily address vascular lesions responsible for alexia.

Pure alexia due to VWFA lesion. Pure alexia is defined as isolated reading impairment, i.e., with preservation of concurrent and writing (Starrfelt and Shallice, 2014). This alexia may be restricted solely to the inability to read words, or, when severe, also prevent the reading of isolated letters, in which case it is referred to as global alexia (Dejerine, 1892). Causal lesions are generally located in the VWFA, in the left fusiform gyrus (Cohen et al., 2003; Marsh and Hillis, 2005; Rodríguez-López et al., 2018). Finally, Cohen and colleagues (2016) report a case of pure alexia occurring after a stroke with VWFA lesion, which they followed for two years, with several behavioral and functional MRI assessments. They observed a gradual improvement in his reading skills through letter-by-letter reading. On functional MRI, there was an increase in activation in bilateral posterior occipital regions associated with increased functional connectivity with language areas, suggesting the existence of other gateways into reading when the VWFA is no longer functional.

Letter-to-letter alexia. When isolated letter identification persists, letter-by-letter reading is possible. Reading time increases with word length, as letters are no longer processed in parallel. This letter-by-letter reading seems to be underpinned by the right hemisphere. Indeed, a patient with alexia following a left occipital hematoma was still able to read letter by letter. However, in the aftermath of a right occipital hematoma, her reading performance deteriorated again, including letter-by-letter, supporting the role of the right occipital cortex in this type of reading (Bartolomeo et al., 1998). Further support for the involvement of the right hemisphere in letter-by-letter reading comes from studies in patients with disconnection syndrome (when the right and left hemispheres no longer communicate; Baynes and Eliassen, 1998) or in a patient with left hemispherectomy (Patterson et al., 1989).

Pure disconnection alexia. In other cases, it is possible to observe alexia in the absence of a VWFA lesion. This is the case when the VWFA is disconnected from visual areas. For example, according to Damasio et Damasio (1983), a left occipital lesion resulting in a right hemianopia, combined with a callosal disconnection, can lead to alexia. Later, Epelbaum and colleagues

(2008) showed that following surgery of an area close to the VWFA, preoperatively identified with functional MRI, the patient became alexic, without a VWFA lesion. However, diffusion rdanalyses showed involution of the arcuate fasciculus and inferior longitudinal fasciculus connecting it to the perisylvian language and primary visual areas respectively.

Impact of distant lesions on the VWFA. As far as reading models are concerned, there is still debate as to which of the various properties reported for the VWFA in functional MRI are the result of local neuronal changes, and which depend solely on "top-down" effects linked to distant connections. One way of finding out would be to study aphasic patients with lesions in the language areas but sparing the left vOTC. The idea would therefore be to study, at the extreme, the VWFA devoid of its "top-down" connections. We could then expect local effects to persist, but all or part of the top-down effects to disappear.

3. Synesthesia

A. General information

i. Definition

Traditionally, synesthesia is defined as a "fusion of the senses": a perception in a given sensory modality (the inducer; Grossenbacher and Lovelace, 2001) will also elicit an experience in another, unsolicited sensory modality (concurrent). The association between the inducer and the concurrent is involuntary and automatic and must also remain stable over time. For example, in grapheme-color synesthesia (GC, **Figure 1.8**), the perception of certain letters will provoke the perception or sensation of colors. For an individual who associates the letter "A" with the color red, the letter "A" will always be associated with red, for example. On the other hand, for another synesthete, the color associated with "A" may be a different color.

Figure 1.8



Figure 1.8. Illustration of a grapheme-color synesthesia, by *Cytowic and Eagleman (2009)*.

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Higher or lower? However, there are situations in which there is no sensory activation strictly speaking. For example, in some synesthesias, the competing stimulus does not involve any of the senses, as in the case of linguistic ordinal personification (LOP), where certain elements of a sequence (numbers, colors, months) evoke a personality. For example, "6 can be perceived as a young man, polite and kind, while 8 is a dignified woman, who acts appropriately, and is married to 9" (Simner and Holenstein, 2007). Secondly, in some synesthetes, thinking about a number or month of the year is enough to trigger the corresponding synesthesia; these synesthetes are named by some authors as "higher synesthetes" (Hubbard et al., 2005; Safran and Sanda, 2015), in contrast to "lower synesthetes" who require sensory perception. A definition of synesthesia circumscribed to sensory perceptions therefore seems too restrictive.

Associator or projector? While the "higher" - "lower" distinction refers to the inducer, the associator - projector distinction concerns the concurrent (Dixon et al., 2004). In associators, the superadded perception is generally described as inside them, "in their mind's eye", whereas in projectors, it is described as outside their body, in the "outside world". For example, in the case of GC synesthesia, where A is associated with the color red, an associative synesthete will have a sensation of red when he sees the letter A, whereas a projector will see the A written in red directly on the page. There is a higher proportion of associative synesthetes than projectors, from 58% to 66% depending on the study (Amsel et al., 2017; Dixon et al., 2004; Gebuis et al., 2009; Nikolić et al., 2007; Rouw and Scholte, 2010). According to some authors, this associator-projector distinction is more of a continuum than a binary distinction (Rouw and Scholte, 2010; Skelton et al., 2009; van Leeuwen et al., 2011).

Acquired synesthesia. Synesthesias are most frequently developmental, but there are a number of cases of acquired synesthesia, sometimes transient with toxic intake (Brogaard, 2013; Luke and Terhune, 2013; Terhune et al., 2014; Van Hout, 2015), but not always: the causes of acquired synesthesia are varied, optic neuritis, retinitis pigmentosa, brain tumor, vascular accident (Afra, 2009; Armel and Ramachandran, 1999).

Finally, we note that, by convention, a synesthesia is first denominated by the inducer (in our example, graphemes), then by the concurrent (in our example, colors).

ii. Synesthesia in numbers

Types of synesthesia. There are at least 70 different types of synesthesias (according to <http://www.daysyn.com/Types-of-Syn.html>; Jewanski et al., 2020), although the precise number is difficult to estimate as inducer-concurrent combinations can be so varied. In a series of 572 synesthetes, Day (2005) describes GC synesthesia as the most frequent, followed by time-color synesthesia (see Table 1.1), in which certain temporal units (such as days of the week, months of the year) are colored. These two synesthesias accounted for over 90% of synesthesias cases in Day's series. In a larger sample of 738 synesthetes, also from Day (and probably including the same sample; Cytowic and Eagleman, 2009), the distribution is similar. These lists of synesthetes are not exhaustive, and any type of association can be imagined: for example, there have been reports of two swimmers in whom a certain style of swimming evoked a specific color (Nikolić et al., 2011).

Prevalence. It is difficult to obtain a reliable estimate of the prevalence of synesthesia in the general population. Nevertheless, at least 4.4% of the population is thought to have one or more synesthesias (Simner et al., 2006). One way of obtaining a reliable estimate in the general population would be a long-term follow-up of a large sample of people and to assess the occurrence of synesthesia. Moreover, as synesthesia is highly varied, an exhaustive questionnaire would be needed. Furthermore, it is known that there is a higher prevalence of synesthesia in certain populations such as artists (Rothen and Meier, 2010), and people with autism spectrum disorder (Baron-Cohen et al., 2013; Dance et al., 2021; Neufeld et al., 2013; Van Leeuwen et al., 2021; Ward and Simner, 2020).

Sex-ratio. Older studies on synesthesia showed a strong preponderance of women (Baron-Cohen et al., 1996; Rich et al., 2005). Ultimately, it seems that there is no gender difference (Simner and Carmichael, 2015) and that the differences found are more generally related to self-referral bias, with women tending to report atypical experiences more spontaneously (Dindia and Allen, 1992).

Synesthesia associations. When one has synesthesia, one is usually apt to have several synesthesias (Ward, 2013), suggesting that there is a common mechanism to the various synesthesias. It is estimated that 40% of synesthetes actually have more than one synesthesia (Ward and Cytowic, 2006). A study in GC synesthetes (Cytowic and Eagleman, 2009) showed

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that the main synesthesia associated was a time-color synesthesia, with people perceiving the days of the week in color. Another study in GC synesthetes also reported more associated sequence-space synesthesia in synesthetes than in controls (Sagiv et al., 2006), in this case number sequences, which they perceive organized in a certain way in space. Simner and Holenstein (2007) also showed that people with OLP synesthesia were up to 10 times more likely to have GC synesthesia than non-synesthetes.

Diagnostic criteria. Diagnostic criteria with test batteries have been developed, notably in the case of synesthesias where the concurrent was a color (Carmichael et al., 2015; Eagleman et al., 2007), but also in taste-shape synesthesias (where a taste evokes a certain shape), or person-smell synesthesias (where mention of a particular person such as mother evokes a certain smell) (Simner et al., 2006). The main diagnostic criterion focuses on the stability and consistency of the association between an inducer and its concurrent, and the test therefore involves a new long-term retest. In these tests, participants are asked for the color associated with different types of inducers, and then the consistency of associations between the different tests is measured. This consistency has also been assessed in young children (Simner et al., 2009), and the longest interval that has validated association consistency is 27 years (Simner and Logie, 2008). Finally, teams have established the validity of the coherence test in a single session (Carmichael et al., 2015; Simner et al., 2006).

Table 1.1

Type	No. synesthetes ^a	%
Colored graphemes	394	68.8
Colored time units	134	23.4
Colored musical sounds	106	18.5
Colored general sounds	82	14.3
Colored musical notes	62	10.8
Colored phonemes	60	10.5
Colored tastes	43	7.5
Colored odors	40	6.9
Colored pain	36	6.3
Colored personalities	26	4.5
Colored touch	25	4.0
Colored temperatures	15	2.6
Colored orgasms	7	1.2
Smell–synesthetic sound	4	0.6
Smell–synesthetic taste	1	0.1
Smell–synesthetic temperature	1	0.1
Smell–synesthetic touch	4	0.6
Sound–synesthetic smell	9	1.5
Sound–synesthetic taste	29	5.0
Sound–synesthetic temperature	4	0.6
Sound–synesthetic touch	25	4.3
Taste–synesthetic sound	1	0.1
Taste–synesthetic temperature	1	0.1
Taste–synesthetic touch	4	0.6
Temperature–synesthetic sound	1	0.1
Touch–synesthetic smell	2	0.3
Touch–synesthetic sound	2	0.3
Touch–synesthetic taste	3	0.5
Touch–synesthetic temperature	1	0.1
Vision–synesthetic smell	6	1.0
Vision–synesthetic sound	6	1.0
Vision–synesthetic taste	11	1.9
Vision–synesthetic temperature	2	0.3
Vision–synesthetic touch	5	0.8
Personality–synesthetic smell	1	0.1

Table 1.1. Report from 572 synesthetes, from publications, e-mails, letters or interviews by S. Day.

Adapted from Day, 2005.

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iii. Synesthesia models

There is no clear model for the mechanisms underlying synesthesia. However, several mechanisms have been proposed (Hubbard and Ramachandran, 2005) to try and explain the phenomenon: in one case, there is an excess of abnormal connection, as in the pruning defect models (Ramachandran and Hubbard, 2001); in the other case, synesthesia relies on a disinhibition mechanism (Grossenbacher and Lovelace, 2001).

Neural pruning defect model. Synaptic density, the number of brain connections and glucose metabolism at the cerebral level are maximal shortly after birth, before decreasing (Chugani et al., 1987; Huttenlocher and Dabholkar, 1997). A certain number of these connections are assumed to be pruned later, during development. If **pruning fails**, normally absent connections between certain brain areas will eventually persist, and these areas, if sensory, may then be co-activated when presented with a type of stimulus. In these models, it is the atypical connections that are responsible for synesthesia (Maurer, 1993). Connected regions may be adjacent, as in GC synesthesia (Hubbard et al., 2006, 2005), and stimulation of the VWFA may result in cross-activation of the color region (V4) by unpruned connections. Indirect arguments in favor of this theory have been made. For example, several cases of synesthesia in children that subsequently regressed have been reported, as if pruning of part of the connections suppressed atypical associations (Simner and Bain, 2013). A genetic study in sound-color synesthetes reports the involvement of several genes in synesthetes. There is also a genetic study in three families of sound-color synesthetes that identified in synesthetes several genes with a role in axogenesis and expressed during infancy (Tilot et al., 2018).

Disinhibition. In the disinhibition hypothesis, there is no abnormality or atypia of connections; structural connectivity is normal. In this hypothesis, it's neurotransmitters that are involved, and the connections responsible are therefore present in everyone, but "functional" only in synesthetes. We can distinguish between remote disinhibition mechanisms and re-entrant processes. The first model is based on associative regions, which are common to different neuronal pathways (Armel and Ramachandran, 1999; Grossenbacher and Lovelace, 2001). They receive feedforward connections from some pathways, but also send feedback to others. These recurrent connections are normally sufficiently inhibited to avoid retrograde stimulation of pathways competing with the one initially involved. In synesthesia, the forward transmission of a signal in the pathway of the inducer to an area where this pathway and that

of the concurrent converge, will enable the retrograde transmission of a signal in the pathway of the concurrent, which will activate a representation of the latter. This retrograde stimulation is made possible by a **disinhibition mechanism**. The second type of model is known as **re-entrant processing** (Smilek et al., 2001). It stipulates, in addition to the presence of connections between the inducer and concurrent regions, the existence of a recurrent connection from a higher processing region (e.g., semantic) to the concurrent region, and generally involves nearby regions ("re-entrant processing"). Finally, the fact that there are transient forms of synesthesia in non-synesthetes (acquired synesthesia) after toxic intake is in favor of a disinhibition mechanism, involving neurotransmitters (Brogaard, 2013; Luke and Terhune, 2013; Terhune et al., 2014; Van Hout, 2015).

In summary, there is no single validated theory concerning the different mechanisms of synesthesia. It is probable that there is not a single exclusive mechanism responsible for all synesthesias in all synesthetes: it is more likely that there is a mixture of these different models, depending on the synesthesia and the synesthete. Moreover, imbalances in the excitation-inhibition balance are likely to give rise to changes in structural connectivity according to the principles of Hebbian plasticity. It is also possible that different aspects and properties of the same synesthesia are underpinned by different mechanisms (Yokoyama et al., 2014). Furthermore, the fact that within the same family, the same synesthete can have different forms of synesthesia would suggest that the same underlying mechanism might be responsible for them (Ward and Simner, 2005). A final distinction may be that developmental synesthesias are linked to an excess of structural connectivity, whereas acquired synesthesias, which often set in more quickly, are linked to a defect in inhibition (Ward and Simner, 2020).

iv. Top-down and bottom-up influences during synesthesia

The role of "top-down" and "bottom-up" processes in synesthesia is unclear. Is conscious access to the inducer's identity necessary to trigger it? Is there a "top-down" modulation of the concurrent's characteristics? According to some authors (Mattingley et al., 2001), synesthesia depends on "top-down" processes and grapheme recognition for color visualization to occur. Others believe, on the contrary, that synesthesia can be triggered without attention to the inducer (Smilek et al., 2001). In another study, during a visual search for a target among distractors, the authors report the case of a number-color synesthete who was less bothered than controls by the increased size of the search field (Palmeri et al., 2002).

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Finally, it would appear that synesthetes have no advantage over controls in a visual search task involving their synesthesia (Edquist et al., 2006; Treisman, 2005). Attention also plays an important role. Depending on the object of the synesthete's attention, the resulting concurrent differs (Rich and Mattingley, 2003): for example, in the case of a GC synesthete, when presented with a "5" written with smaller "3s" (**Figure 1.9**), if the synesthete focuses his attention on the overall 5, then he will perceive the color associated with the 5, whereas if he focuses it on the 3s making it up, he will see the color associated with the 3 (Ramachandran and Hubbard, 2001). The same authors also report another example with an ambiguous orthographic stimulus between an H and an A (Figure 1.9), and interpreted according to the word in which it is inserted. Synesthetic color therefore varies for the same stimulus, depending on context. The proportion of "top-down" and "bottom-up" influences seems to be correlated with projector-associator status (van Leeuwen et al., 2011).

Figure 1.9



Figure 1.9. Examples of stimuli where synesthetic perception is modified by "top-down" influences.

Adapted from Ramachandran and Hubbard, 2001.

Finally, Cytowic and Eagleman (2009) reported another interesting case of a GC synesthete whose colors associated with the letters of the word "phthalocyanine" changed after she learned the meaning of the word (**Figure 1.10**), highlighting the influence of semantics and therefore "top-down" connections on concurrent features.

Figure 1.10

PHTHALOCYANINE

PHTHALOCYANINE

Figure 1.10. Top line shows the synesthetic perception by a synesthete of the word phthalocyanine before learning the meaning of the word. Bottom shows the perception by the same synesthete after learning the meaning of phthalocyanine. After *Cytowic and Eagleman (2009)*.

v. Origin of synesthesia

A genetic component

A genetic origin for synesthesia is likely, given the high prevalence in families of synesthetes, estimated at between 33% and 42% (Barnett et al., 2008; Baron-Cohen et al., 1996). There is no clearly identified candidate gene, but studies comparing synesthetes to non-synesthetes within the same family have confirmed differences between the two groups (Asher et al., 2009; Tomson et al., 2011). Despite the genetic influence, a case of discordance has been reported in twin girls, with digit-color synesthesia in one and no synesthesia in the other (Smilek et al., 2002). It has also been shown that not all synesthetes in the same family have the same type of synesthesia (Ward et al., 2005), nor do they have the same inducer-concurrent associations for a given synesthesia (Barnett et al., 2008). A large number of chromosomal regions have been identified, suggesting a complex, non-Mendelian hereditary mechanism, and the involvement of other components.

Role of the environment

The role of the environment in the development of synesthesia is not negligible. It could explain previously mentioned reports, such as the case of discordant twins, or different associations within the same family, which show that genetics is not enough to explain the whole phenomenon. Numerous studies report cases of pseudo-synesthesia, which appeared

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after participants had been trained (Colizoli et al., 2014, 2012). Rothen et al (2018) also successfully trained non-synesthetes, and showed that this conditioning resulted in an increase in cortical excitability in regions involved in synesthesia, and not in those not involved. The onset of synesthesia can therefore be favored by the environment, but so can the nature of the association. For example, Witthoft and Winawer (2006) reported a case of GC synesthesia in which the color of associations was directly related to the color of letters magnetized on his refrigerator during childhood. They also later reported 11 similar cases, where synesthesia associations were linked to toys with colored letters during childhood (Witthoft and Winawer, 2013). There is in fact another model of synesthesias, known as "**locking-in**", in which a synesthesia is simply the result of past exposure to an association between an inducer and a concurrent (Root et al., 2019). For example, in the case of GC synesthesia, the color associated with a given grapheme results from past exposure to this association and will therefore be "random" in non-synesthetes because it is generated in the moment. This perspective echoes memory theories (Chiou and Rich, 2014; Witthoft and Winawer, 2013), according to which synesthesia would be an access to memories, and associations from past experiences. The locking-in model also echoes the theory of plasticity in synesthesia, according to which synesthetes may have less plasticity, justifying the fact that once an association has been established between an inducer and a concurrent, low brain plasticity is responsible for its persistence (Cytowic and Eagleman, 2009), although other authors instead report increased plasticity in synesthetes (Shraki et al., 2016). These associations can be traced back to personalized and contextual individual experience but can also be secondary to more generalized and impersonal associations: for example, in GC synesthesia, associations are not random, and the most frequent letters are associated with the most frequent color terms (Berlin and Kay, 1991; Simner et al., 2005). Numbers, on the other hand, are learned in order (unlike letters, where the most frequent are learned first), and in number-color synesthesia, it's the numbers learned first and therefore the smallest that are associated with the most frequent color terms (Shanon, 1982). Finally, there may also be lexico-gustatory synesthesias strongly influenced by the semantic and phonological aspects of the inducers (Ward and Simner, 2003), such as the word "bar" tasting like milk chocolate, or the name "Virginia" tasting like vinegar.

Overall, the origin of synesthesia (or rather, the origins of synesthesias) has not been deciphered. It seems that several types of components play a role, having an impact at different levels of synesthesia: the existence or non-existence of synesthesia, the modalities involved, and/or the associations within these modalities. Although certain genes have been identified in families of synesthetes, there is no evidence of Mendelian inheritance, and the form of synesthesia remains as much determined by the environment, past experiences, and sometimes even phonological-semantic characteristics.

B. Anatomical correlates

Firstly, it's difficult to be exhaustive in presenting the anatomical correlates of synesthesia, so many different ones exist, but we can infer more or less generalizable principles from the study of certain specific synesthesias. There is probably a global overconnectivity, whether structural or functional (Ward, 2019), and depending on the inducer and concurrent of synesthesia, the involvement of certain corresponding regions can be found. Secondly, many studies have attempted to pinpoint the involvement of some regions in synesthesia, but the results are inconsistent. It is possible that one of the causes of these difficulties is the small size of some of these studies (Hupé and Dojat, 2015), linked to the relative difficulties in recruiting synesthetes, but also the variability of the synesthetic phenomenon and perhaps the underlying mechanism among the participants.

i. Functional imaging

The first study was in PET in the context of word-color synesthesia (Paulesu et al., 1995), and showed greater activations in synesthetes during word listening in color integration regions, in posterior inferior temporal, but not in low-level visual regions such as V4. On the contrary, other studies have subsequently shown in functional MRI activations during word listening in V4 color regions or in primary visual cortex (Aleman et al., 2001; Gray et al., 2006; Nunn et al., 2002; Weiss et al., 2001). Similarly, in the context of GC synesthesia, some studies have failed to demonstrate V4 activation (Rich et al., 2006), while others have shown V4 activation in a synesthete with acquired blindness when reading Braille (Steven et al., 2006), or V4 activation in a group of synesthetes when reading certain graphemes, compared with a group of controls (Sperling et al., 2006). More recently, Yong et al., (2017) also showed, in a person with auditory-visual synesthesia secondary to blindness, activations in primary and secondary

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visual areas when perceiving phosphene-triggering sounds, compared with a non-synesthetic control. In addition to activations in areas corresponding to the concurrent's perception, we can also ask whether the concurrent's synesthetic perception and its "real" perception are responsible for activations in the same areas. Here again, in the context of GC synesthesia, the results are discordant: Nunn et al. (2002) report activations in the same regions, whereas in two other studies, the regions activated are different depending on whether the perception is synesthetic or "real" (Hupé et al., 2012; Van Leeuwen et al., 2010).

ii. Transcranial magnetic stimulation

Another interesting way of highlighting the causal role of a region in a given process is to disrupt the functioning of this region by stimulating it and observing the consequences. This is what several teams have done using TMS (Esterman et al., 2006; Muggleton et al., 2007), stimulating the right occipito-parietal cortex, an associative region, resulting in the disruption of GC synesthesia, and thus suggesting a role for this region in GC synesthesia.

iii. Structural analysis

Connectivity. One of the main models underlying the phenomenon of synesthesia is based on an increase in structural connectivity. To support this model, many authors have studied connectivity in synesthetes. Rouw and Scholte (2007) showed in 18 GC synesthetes an increase in FA in several bilateral fronto-temporo-parietal regions, including one in the right inferior temporal, close to the inferior longitudinal fasciculus, connecting the occipital regions (including V4) to the temporal lobe (Catani, 2003). This same cluster also had higher FA values in projector synesthetes than in associators. Differences in FA were also demonstrated in 10 music-color synesthetes in the right inferior occipito-frontal cluster, whose FA was higher in synesthetes (Zamm et al., 2013). Although differences in structural connectivity have been demonstrated in synesthetes, it remains unclear whether they are the cause of the phenomenon, or the consequence of disinhibition via plasticity mechanisms.

Morphometry. Morphometric differences have been reported between synesthetes and controls. There is an increase in gray matter density in the V4 and parietal regions in GC synesthesia (Pascual-Leone et al., 2005). Gray matter volume is also increased in somatosensory cortex in visuo-tactile synesthesia ("mirror touch"; Holle et al., 2013). Other studies have also shown differences in cortical thickness volume and surface area in

synesthetes (Banissy et al., 2012; Weiss and Fink, 2009). For example in GC synesthesia, there were increases for these measures in the right and left fusiform gyrus (Jäncke et al., 2009)

In summary, the results as a whole are discordant in terms of functional analysis, probably linked to sample sizes that were too small, unfortunately difficult to avoid. TMS and the study of white and grey substances show less discrepant results, but have been poorly replicated, and sample sizes are also small.

4. Tickertape synesthesia

Definition. A little-studied synesthesia known as tickertape synesthesia (TTS) was described as early as 1883 (Galton, 1883). People with TTS automatically see all the words they hear written down. Galton already noted that the phenomenon differed from synesthete to synesthete, in terms of font size and color. This synesthesia therefore has the particularity of involving language as both inducer and concurrent. It links speech with reading and represents a particularly interesting angle of study of the influences of speech on reading.

A. Knowledge from the literature

Only two group studies have been done on TTS, addressing phenomenological and behavioral aspects (Chun and Hupé, 2013; Holm et al., 2015).

Epidemiology

The prevalence of TTS is estimated at 7% according to Chun and Hupé. In their study, the estimate is based on the number of leaflets distributed to recruit their participants, of which only 30% responded. This prevalence is the lowest possible estimate from their data, but their diagnostic criterion is based solely on self-referral.

Prevalence is more variable according to Holm et al. (2015). They distributed leaflets in a museum, cinema, on social networks and at university, and analyzed the responses of 425 participants. They asked participants about the appearance of subtitles in different circumstances: when they heard people talking, when they themselves spoke aloud or when they were thinking; and also collected the systematic nature of the appearance of these subtitles. According to the responses, among those having subtitles for all 3 inducers, participants were classified as obligatory (1.4%), involuntary (8.7%) or voluntary (4.7%)

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synesthetes, depending on whether the 3 inducers triggered synesthesia almost always, whether the 3 inducers triggered it at least effortlessly, or whether the participant visualized subtitles voluntarily for all 3 inducers respectively. Other intermediate categories are also described depending on the different responses according to inducers. The total prevalence is therefore at least 1.4% when the strictest criteria are used but may be higher if less automatic categories of synesthetes are included. The authors report that 43.3% of participants never had subtitles for any of the inducers, suggesting that some degree of orthographic visualization is more common than none at all.

In both studies, there was no difference in prevalence between men and women. In the Holm et al. study, there was also no relationship with age or level of education.

Phenomenological description

Chun and Hupé (2013) were able to collect subjective descriptions of TTS from a subgroup of the participants in their study. They thus report certain features of perception during TTS. In most cases, size and font are stable among participants, although some may vary in size according to sound volume. The way in which "subtitles" are presented is also variable: it can be fixed, as on a screen, or dynamic, coming out of the speaker's mouth. Finally, some participants reported the persistence of synesthesia with the visualization of a phonological transcript when listening to unfamiliar foreign languages, or a visualization of onomatopoeia "like in cartoons" when listening to certain noises.

Holm et al. (2015) also collected phenomenological data on TTS for certain subgroups, and also found some variability: handwritten or printed writing, moving text, subtitles for foreign languages or colored letters. They also looked at a number of specific situations: for example, when several conversations are taking place at the same time, is this a source of confusion? Is there a visualization of a hand writing when viewing subtitles? Finally, according to their study, the main drawback reported with TTS is the interference of their synesthesia with certain visual perceptions, or discomfort during multiple conversations. Most of their participants report a benefit from TTS, but the nature of this benefit is not reported.

Behavioral performance

Only Holm et al. (2015) have investigated a behavioral aspect of this synesthesia, although in practice they did not administer a test. They asked a proportion of their participants whether they had any particular ability to give the exact number of letters in a long-overheard word, or to spell or repeat an overheard word backwards. Only one participant replied that he thought he had a particular aptitude for counting the number of letters when listening to a long word, while 5 and 4% were able to spell and repeat a word backwards respectively.

These two studies are complemented by a few case reports: that of a 39-year-old patient followed in psychiatry for schizophrenia (Bastiampillai et al., 2014), with TTS since he was 6 years old, which the authors potentially link to a temporal arachnoid cyst; another unreported case (Price and Mykland, 2013), but briefly described by Holm et al. (2015), of a young woman described as having particular abilities to list the letters of a word, and whose synesthesia was triggered by her own speech or thoughts; the case of another young woman able to pronounce words or sequences of words backwards because she visualized them (Coltheart and Glick, 1974).

Overall, subtitle synesthesia is therefore a little-studied phenomenon, although it has long been described, and offers a new line of investigation into the links between the speech and reading systems. There are some epidemiological, phenomenological, and behavioral data, but no anatomical-clinical correlation studies.

Hypothesis. Our hypothesis is that this synesthesia results from a reverse activation of the reading network, which transforms sounds into orthographic representations. This activation would be the consequence of a "top-down" influence of phonological and lexical representations on the orthographic representation. The regions underlying this phenomenon should therefore overlap with the orthographic and language networks.

Objectives. By studying TTS, we aim to 1/ better characterize certain aspects, notably visuo-spatial, of this synesthesia; 2/ try to objectify the phenomenon, using behavioral tests to

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highlight differences between tickertapers and control subjects, on tasks where synesthesia would represent an advantage, and on others where it would represent a disadvantage; 3/ using functional imaging, better characterize the cortical regions involved in the phenomenon, and thus clarify the role of these regions in current language models.

We have studied various aspects of tickertape synesthesia.

The first part of this work presents the case of a TTS synesthete, whom we studied with functional MRI in order to identify the cortical networks involved in TTS. In an auditory experiment, we presented him with right-side-up and upside-down language; in a second experiment, we presented him with lists of words, and pseudowords. Finally, we used dynamic causal modeling to analyze the temporality of activations of the different regions involved.

Secondly, we were able to recruit 26 TTS synesthetes, and had them complete a questionnaire aimed at describing their synesthesia. We collected subjective descriptions of their synesthesia, including visual and temporal aspects, and the conditions or inducers likely to trigger synesthesia. We also asked them to describe their synesthesia in specific situations likely to create confusion (when reading or watching a film with subtitles, for example).

Next, we investigated whether it was possible to objectify a behavioral advantage or handicap in certain behavioral tests for TTS. We administered these tests to a subgroup of 22 participants. The first 3 tests were based on orthographic working memory, and the next 2 tests involved a visual task, with concurrent auditory stimulation.

We also took functional MRI images of the 17 right-handed participants in this same subgroup, to identify the cortical networks underlying synesthesia. We auditorily presented them with sentences, lists of words, pseudowords and numbers, and noise (Experiment 1). Then we presented them with visual images and written words (Experiment 2). Finally, we also imaged them on resting-state functional MRI (Experiment 3). We compared the 2 groups for each of these different experiments.

Finally, the last section presents the case of a patient with posterior reversible encephalopathy syndrome (PRES), resulting in extensive lesions of the occipital regions, preserving the primary visual cortex, but manifesting as cortical blindness. This patient was studied using visual evoked potentials and functional MRI with a presentation task of different types of images, as well as resting-state functional MRI, to study activations within his visual cortex and differences in connections between him and a control group.

CHAPTER II

A single case neuroimaging study of tickertape synesthesia



OPEN **A single case neuroimaging study of tickertape synesthesia**

Fabien Hauw^{1,2✉}, Mohamed El Soudany¹, Charlotte Rosso^{1,3}, Jean Daunizeau¹ & Laurent Cohen^{1,2}

Reading acquisition is enabled by deep changes in the brain's visual system and language areas, and in the links subtending their collaboration. Disruption of those plastic processes commonly results in developmental dyslexia. However, atypical development of reading mechanisms may occasionally result in ticker-tape synesthesia (TTS), a condition described by Francis Galton in 1883 wherein individuals "see mentally in print every word that is uttered (...) as from a long imaginary strip of paper". While reading is the bottom-up translation of letters into speech, TTS may be viewed as its opposite, the top-down translation of speech into internally visualized letters. In a series of functional MRI experiments, we studied MK, a man with TTS. We showed that a set of left-hemispheric areas were more active in MK than in controls during the perception of normal than reversed speech, including frontoparietal areas involved in speech processing, and the Visual Word Form Area, an occipitotemporal region subtending orthography. Those areas were identical to those involved in reading, supporting the construal of TTS as upended reading. Using dynamic causal modeling, we further showed that, parallel to reading, TTS induced by spoken words and pseudowords relied on top-down flow of information along distinct lexical and phonological routes, involving the middle temporal and supramarginal gyri, respectively. Future studies of TTS should shed new light on the neurodevelopmental mechanisms of reading acquisition, their variability and their disorders.

Reading acquisition is enabled by deep functional and anatomical changes in the brain's visual system and language areas, and in the links that subtend their collaboration¹⁻⁴. Whenever those delicate plasticity processes are compromised, various sorts of developmental dyslexia may result^{5,6}.

However, atypical development of reading mechanisms may occasionally result in another condition, in some sense opposite to dyslexia, one which has not received sufficient scientific attention. The polymath Francis Galton noted in 1883 that "some few persons see mentally in print every word that is uttered and they read them off usually as from a long imaginary strip of paper, such as is unwound from telegraphic instruments"⁷. This unusual phenomenon, was dubbed by Galton ticker-tape synesthesia (TTS). TTS, once purely anecdotal, actually touches on the core of the brain mechanisms of normal and impaired reading. Indeed, while reading is the translation of visual letters into speech, TTS may be viewed as its exact opposite, i.e. the translation of speech into internally visualized letters, respectively the "inducer" and "concurrent" in synesthesia parlance^{8,9}.

More generally, synesthesia encompasses a range of subjective phenomena in which stimulation in one sensory or cognitive domain (the inducer) automatically triggers additional perceptions in one or several other unstimulated domains (the concurrent). For example, in grapheme-color synesthesia, one of the most studied synesthesia, digits and letters, printed or even imagined, are perceived as colored¹⁰.

During word reading, letters and their order are first identified in the Visual Word Form Area (VWFA), a reproducible sector of the left ventral occipitotemporal (VOT) cortex, whose lesion yields pure alexia^{1,11,12}. Orthographic information is then broadcast to language areas, giving access to the associated sounds (the "phonological route") and meaning (the "lexico-semantic route")¹³⁻¹⁵. Reciprocally to this "bottom-up" spread of information, brain imaging revealed that in literate individuals, language areas exert "top-down" influences upon orthographic representations. Thus, attended speech activates the VOT cortex including the VWFA¹⁶⁻¹⁸, and language areas send different top-down influences to the VWFA during the reading of real words and of pseudowords¹⁹. In this framework, as first hypothesized by Holm et al.⁸, TTS would reflect exceptionally powerful and automatic top-down influences from speech processing areas onto the VWFA.

This connectivity hypothesis of TTS is compatible with most neuroscientific theories of synesthesia, which all propose increased connectivity as a core mechanism⁹. According to the pruning theory²⁰, some connections

¹Inserm U 1127, CNRS UMR 7225, Sorbonne Universités, Institut du Cerveau, ICM, Paris, France. ²AP-HP, Hôpital de la Pitié Salpêtrière, Fédération de Neurologie, Paris, France. ³AP-HP, Urgences Cérébro-Vasculaires, Hôpital Pitié-Salpêtrière, Paris, France. ✉email: fabien.hauw@orange.fr

A single case neuroimaging study of tickertape synesthesia

Fabien Hauw^{a, b}, Mohamed El Soudany^a, Charlotte Rosso^{a, c},

Jean Daunizeau^a, Laurent Cohen^{a, b}

a. Inserm U 1127, CNRS UMR 7225, Sorbonne Universités, Institut du Cerveau, ICM, Paris, France

b. AP-HP, Hôpital de La Pitié Salpêtrière, Fédération de Neurologie, Paris, France

c. AP-HP, Urgences Cérébro-Vasculaires, Hôpital Pitié-Salpêtrière, Paris, France

1. Abstract

Reading acquisition is enabled by deep changes in the brain's visual system and language areas, and in the links subtending their collaboration. Disruption of those plastic processes commonly results in developmental dyslexia. However, atypical development of reading mechanisms may occasionally result in tickertape synesthesia (TTS), a condition described by Francis Galton in 1883 wherein individuals "see mentally in print every word that is uttered (...) as from a long imaginary strip of paper". While reading is the bottom-up translation of letters into speech, TTS may be viewed as its opposite, the top-down translation of speech into internally visualized letters. In a series of functional MRI experiments, we studied MK, a man with TTS. We showed that a set of left-hemispheric areas were more active in MK than in controls during the perception of normal than reversed speech, including frontoparietal areas involved in speech processing, and the Visual Word Form Area, an occipitotemporal region subtending orthography. Those areas were identical to those involved in reading, supporting the construal of TTS as upended reading. Using dynamic causal modeling, we further showed that, parallel to reading, TTS induced by spoken words and pseudowords relied on top-down flow of information along distinct lexical and phonological routes, involving the middle temporal and supramarginal gyri, respectively. Future studies of TTS

should shed new light on the neurodevelopmental mechanisms of reading acquisition, their variability and their disorders.

2. Introduction

Reading acquisition is enabled by deep functional and anatomical changes in the brain's visual system and language areas, and in the links that subtend their collaboration (Dehaene et al., 2015; Dehaene-Lambertz et al., 2018; López-Barroso et al., 2020; Thiebaut de Schotten et al., 2014). Whenever those delicate plasticity processes are compromised, various sorts of developmental dyslexia may result (D'Mello and Gabrieli, 2018; Friedmann and Coltheart, 2018).

However, atypical development of reading mechanisms may occasionally result in another condition, in some sense opposite to dyslexia, one which has not received sufficient scientific attention. The polymath Francis Galton noted in 1883 that "some few persons see mentally in print every word that is uttered and they read them off usually as from a long imaginary strip of paper, such as is unwound from telegraphic instruments" (Galton, 1883). This unusual phenomenon, was dubbed by Galton tickertape synesthesia (TTS). TTS, once purely anecdotal, actually touches on the core of the brain mechanisms of normal and impaired reading. Indeed, while reading is the translation of visual letters into speech, TTS may be viewed as its exact opposite, i.e. the translation of speech into internally visualized letters, respectively the "inducer" and "concurrent" in synesthesia parlance (Holm et al., 2015; Ward and Simner, 2020).

More generally, synesthesia encompasses a range of subjective phenomena in which stimulation in one sensory or cognitive domain (the inducer) automatically triggers additional perceptions in one or several other unstimulated domains (the concurrent). For example, in grapheme-color synesthesia, one of the most studied synesthesia, digits and letters, printed or even imagined, are perceived as colored (Simner and Bain, 2013).

During word reading, letters and their order are first identified in the Visual Word Form Area (VWFA), a reproducible sector of the left ventral occipitotemporal (VOT) cortex, whose lesion yields pure alexia (Cohen et al., 2000; Dehaene et al., 2015; Dejerine, 1892). Orthographic information is then broadcast to language areas, giving access to the associated sounds (the

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“phonological route”) and meaning (the “lexico-semantic route”) (Coltheart, 2012; Perry et al., 2007; J. S. Taylor et al., 2013). Reciprocally to this “bottom-up” spread of information, brain imaging revealed that in literate individuals, language areas exert “top-down” influences upon orthographic representations. Thus, attended speech activates the VOT cortex including the VWFA (Cohen et al., 2021; Ludersdorfer et al., 2016; Yoncheva et al., 2010), and language areas send different top-down influences to the VWFA during the reading of real words and of pseudowords (Sharoh et al., 2019). In this framework, as first hypothesized by Holm et al. (2015), TTS would reflect exceptionally powerful and automatic top-down influences from speech processing areas onto the VWFA.

This connectivity hypothesis of TTS is compatible with most neuroscientific theories of synesthesia, which all propose increased connectivity as a core mechanism (Ward and Simner, 2020). According to the pruning theory (Spector and Maurer, 2009), some connections present in children are not pruned and then are responsible for the persistence of atypical anatomical connections in adults. Alternative theories rather support atypical functional connectivity, particularly disinhibition of the links from inducer to concurrent (Grossenbacher and Lovelace, 2001).

Using functional MRI (fMRI) in a man in whom TTS was triggered by both real words and pseudowords, we assessed the hypothesis that TTS would essentially upend the reading system to generate letters from sound.

We implemented this hypothesis as the following four specific predictions. (1) TTS should activate perisylvian language areas involved in speech processing and phonology-to-orthography translation, and VOT regions subtending orthography. (2) Regions involved in TTS should overlap with those involved in reading. (3) Assuming that TTS reflects intense top-down flow of information in the reading system, dynamic models should reveal an increased drive of the reading system by speech input. (4) Due to the overarching distinction between the lexical and phonological routes, top-down influences should follow different paths within the reading system depending on whether synesthesia is triggered by words or pseudowords.

3. Materials and Methods

A. A case of tickertape synesthesia

MK was a 69 years old man, right-handed, native French speaker, a still active engineer and researcher in the field of radar technology, with no significant medical history. For as long as he could remember, when listening to speech, he had been simultaneously perceiving the words in their written form. About a year before the present study, while talking with friends, he accidentally discovered that this phenomenon was quite unusual. He knew about our scientific interest in reading from the media and contacted one of us out of curiosity. TTS was triggered by speech perception, irrespective of whether it was somebody else or MK himself speaking, of whether he could see the face of the speaker or not, of whether he was himself speaking overtly or covertly “in his head”.

During TTS, MK felt that he perceived distinctly each and every letter. Mental images of words did not occupy a well-defined position in external space, but were rather “in his head”; still they looked black, and could be in upper or lower case. Size was “normal, as when you’re reading”. He felt that he perceived about one word at a time. The illusion appeared immediately upon speech onset and persisted briefly after speech ended. TTS was unaffected by the voice, the gender, or the emotion of the speaker, nor by the content of the utterance. It occurred even with unattended speech, such as from neighbor travelers on a train. MK could not voluntarily inhibit TTS, and found parasitic speech quite disturbing when he was reading, although this may be a common nuisance. MK enjoyed listening to wordless music, which generated no TTS. He had no other associated type of synesthesia. His daughter and a niece were subject to the same phenomenon (Tilot et al., 2018).

B. Controls

We compared MK to two groups of healthy typical controls, whose data were collected in the context of other protocols unrelated to synesthesia. One group (G1) included 22 participants, aged 20-36 years (median 28 years, 10 men). The other group (G2) included 14 older controls, aged 51-75 years (median 64 years, 5 men). All participants were native French speakers, right-handed according to the Edinburgh Inventory (Oldfield, 1971), had no history of neurological or psychiatric disorders. The research was approved by the institutional review

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board of the Institut national de la santé et de la recherche médicale (protocols C10_50 and C13-41), and all participants provided informed written consent. All studies were carried out in accordance with the Declaration of Helsinki.

C. Experiment 1: Normal and reversed speech perception

i. Stimuli and procedure

The Red Riding Hood story was recorded with a female voice, and a time-reversed version of the recording was derived by playing it backward. MK and group G1 received a pseudo-random alternation of 6 blocks of normal and 6 blocks of reversed speech (block duration 15 seconds), separated with silent rest periods, for a total of 5 min and 12 s. Group G2 received a slightly shorter version (4 normal and 5 reversed blocks, for a total of 4 min and 15 s). Participants were simply asked to pay attention to the story.

ii. MRI acquisition

For MK and G1, multi-echo (ME) fMRI images (Posse, 2012) were acquired on a Siemens 3T MAGNETOM Prisma scanner, with a 20-channel receive-only head coil: TR 1.3 s; multi-TE 15, 34.24, 53.48 ms; flip angle 68°; voxel size 3 × 3 × 3 mm; 48 slices. An anatomical T1-weighted image was acquired: TR 2.3 s; TE 2.76 ms; flip angle 9°; voxel size 1 × 1 × 1 mm). For G2, single-echo sequences were acquired on a Siemens 3T MAGNETOM Verio scanner, with a 20-channel receive-only head coil: TR 3 s; TE 25 ms; flip angle 90°; voxel size 2 × 2 × 2.5 mm; 49 slices. An anatomical T1-weighted image was acquired: TR 2.3 s; TE 4.18 ms; flip angle 9°; voxel size 1 × 1 × 1 mm).

iii. Preprocessing

For MK and G1, using `afni_proc.py`, all echo timeseries were slice-time corrected, motion correction was computed on the first echo and applied to all echos, and echo images were merged using `t2smmap.py` from the `meica.py` toolbox provided with AFNI: <http://afni.nimh.nih.gov/afni/>. Then, using SPM12 (Wellcome Institute of Imaging Neuroscience, London, UK) implemented in Matlab, functional time-series were co-registered to the anatomical volume, normalized, resampled to 3 mm cubic voxels, and spatially smoothed (6 mm FWHM). For G2, time-series were preprocessed only with SPM12, following

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the same steps: slice-timing, realignment, co-registration to the anatomy, normalization, resampling to 3 mm cubic voxels, smoothing (6mm FWHM).

iv. Regions of interest

In addition to the whole-brain approach, we restricted some analyses within two a priori defined regions of interest (ROI). First, we used a 8 mm radius sphere centered at the peak of the VWFA (MNI -44 -50 -14), as identified in Dehaene et al. (2010b). Second, we created a ROI covering left-hemispheric language areas and VOT cortex (Supplementary Figure S2.1), by merging the opercular and triangular parts of the inferior frontal gyrus, the supplementary motor area, the precentral, fusiform, inferior parietal, supramarginal, angular, superior and middle temporal, and inferior temporal gyri, as defined in the AAL 3 atlas (Rolls et al., 2020).

v. Statistical analysis

One subject was excluded due to technical issues during acquisition. For single-subject analyses, we used a general linear model (GLM) including regressors for normal and reversed speech, convolved with the canonical SPM hemodynamic response function (HRF), plus 6 motion parameters, and high-pass filtering (128 s cutoff). For second-level analyses, we used two sample t-tests to assess differences between MK and control participants, with age as a covariate. We set both the first- and second-level voxel-wise cluster-forming threshold to $p < 0.001$, and the cluster-wise threshold to $p < 0.05$ corrected for multiple comparisons across the whole brain or within ROIs. In the text and in Tables, we provide Z-scores for contrasts of interest at peak activation voxels.

D. Experiment 2: Visual localizer

i. Stimuli and procedure

Only MK participated in this experiment. He was presented with an alternation of blocks of pictures (8s per block) and periods of rest (7.8 s per period). Each stimulation block included eight pictures from one of the following categories: printed words, numbers, faces, houses, tools, body parts. Each picture was displayed for 600 ms and followed by a 400 ms blank screen. During rest and inter-trials intervals, a black central fixation cross was presented to minimize eye-movements. The experiment included 10 s of initial rest, followed by 30 blocks

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of pictures (six for each category) and 30 periods of rest. Blocks were presented in pseudorandom order to maximize the variety of transitions between conditions while avoiding repetition of the same condition in successive blocks. Participants were asked to press a button with their right thumb whenever a picture was identical to the previous one, which was the case for 20% of stimuli (1-3 repetitions/block).

ii. MRI acquisition, preprocessing, and statistical analysis

Functional images were acquired on a Siemens 3T MAGNETOM Verio scanner equipped with a 64-channel receive-only head coil: TR 1022 ms; TE 25 ms; flip angle 62°; voxel size 2.5 × 2.5 × 3 mm; 45 slices. Preprocessing was the same as for single-echo data in Experiment 1. Statistical analysis and thresholding followed the same method as in Experiment 1, apart from the definition of regressors of interest: here we defined one regressor for each of the 5 categories of stimuli, plus a regressor for responses to targets.

E. Experiment 3: Listening to words and pseudowords

i. Stimuli and procedure

MK and the G1 group of control subjects participated in this experiment. We generated a list of 64 words and 32 pseudowords matched in number of phonemes and syllables. Real words included 32 high- and 32 low-frequency words, whose activation pattern did not differ, and which were averaged in all analyzes. Stimuli were synthesized with a female French voice, and equated for maximum amplitude. Stimuli had a mean duration of 644 ms, with no difference between words and pseudowords.

Stimuli were organized in 48 mini-blocks of 8 stimuli each. Mini-blocks were grouped in 8 consecutive blocks, each composed of 2 mini-blocks of PW and 4 mini-blocks of words. The run started and ended with a 15 seconds silence, and an additional 15 seconds pause was present between blocks. The total duration was about 12 minutes. Subjects had to detect the occasional target pseudoword “tatatata”, pronounced by the same voice as stimuli.

ii. MRI acquisition, preprocessing, and statistical analysis

Acquisition and preprocessing were the same as for multi-echo data in Experiment 1. Univariate analyses and thresholding followed the same method as in Experiment 1, apart

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from the definition of regressors of interest: here we defined regressors for low-frequency words, high-frequency words, pseudowords, targets and responses to targets. As controls were all younger than MK, an age regressor would have absorbed any difference between the two. Hence no age regressor was included in second-level analyses. Moreover, multivariate pattern analyses (MVPA) were conducted using The Decoding Toolbox (Hebart et al., 2015), in order to decode words from pseudowords. To train and test the support vector machine, we performed 8 leave-one-block-out cross validation folds, across the 8 blocks of the experiment. Decoding was performed across the volume activated by the averaged words and pseudowords (voxelwise $p < 0.01$), using a 12mm radius searchlight. Decoding performance around each voxel was quantified as the “area under the curve” (AUC) of signal-detection theory. In order to assess the significance of decoding accuracy in individual participants, we computed a permutation test, with a total of 128 permutations. We report voxels with better-than-chance decoding performance ($p < 0.05$), with moreover an ad-hoc minimum cluster size of 50 voxels.

F. Dynamic Causal Modelling (DCM)

We performed deterministic DCM analysis on Experiments 1 and 3, using the DCM toolbox implemented in SPM12. First, a GLM was defined for each experiment, with one regressor modeling all auditory stimulations, plus a parametric modulator taking the value +1 or -1 for normal and reversed speech in Experiment 1, and the value +1 or -1 for words and pseudowords in Experiment 3. Time series were extracted from 4 ROIs identified in Experiments 1 to 3: (1) The mid superior temporal gyrus ROI (STGm) was defined as a 6mm radius sphere centered on the activation peak of reversed speech > rest in controls in Experiment 1; (2) The supra-marginal gyrus ROI (SMG) was the cluster, identified in the contrast normal speech > reversed speech in MK > controls in Experiment 1; (3) The middle temporal ROI (MTG) was the cluster of effective lexicality decoding in MK in Experiment 3; (4) The VWFA was defined as a 6mm radius sphere centered on the activation peak of words > faces and houses in MK in Experiment 2. The VWFA and STG ROIs were defined as spheres because activation clusters were large and extended to adjacent irrelevant regions. We specified a set of a priori constraints on the connections between the 4 regions (defining possible model “families”), and on the modulations acting on those connections, as fully presented in the Results section. In MK, within those constraints, we successively identified

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for each experiment, (1) the most likely set of intrinsic connections between ROIs, and (2) the most likely pattern of modulation of those connections by experimental factors. In brief, we pooled models into model families, each of which shares the same intrinsic connectivity pattern. Within each family, different models then corresponded to different connectivity modulation patterns.

4. Results

G. Experiment 1: The correlates of tickertape synesthesia during speech perception

We first scanned MK with fMRI while he was listening to continuous speech (the Red Riding Hood story), to time-reversed speech as a control for low-level auditory perception, and while he was at rest, and his activations were compared to neurotypical controls (see Methods). As expected, MK reported that listening to normal speech induced vivid synesthesia, while reversed speech did not generate orthographic imagery.

In controls, reversed speech minus rest activated the bilateral mid-superior temporal gyrus (STG), inferior frontal gyrus (IFG) and supplemental motor area (SMA), and the left precentral gyrus (Figure 2.1 and Table S2.1). The contrast of normal minus reversed speech additionally activated the bilateral left-predominant IFG and superior temporal sulcus (STS) from the temporal pole to the angular gyrus (AG), the left precentral cortex, the bilateral SMA and precuneus, plus the VOT cortex along the lateral occipitotemporal sulcus anterior to MNI Y=-62 (Figure 2.1 and Table S2.1).

Figure 2.1

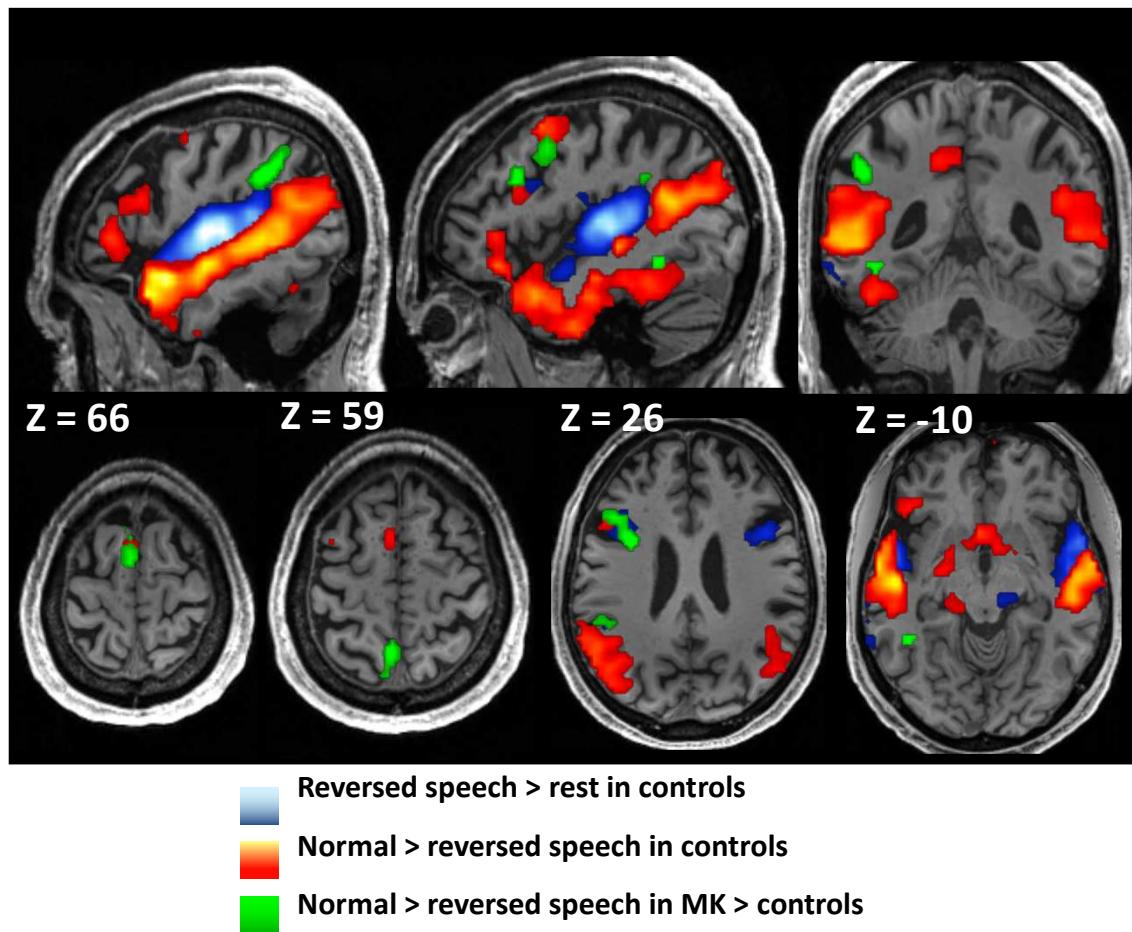


Figure 2.1. Experiment 1: Correlates of tickertape synesthesia (TTS) during speech perception. Activation in control participants by reversed speech minus rest (blue), and by normal minus reversed speech (hot colors). The latter included left-predominant perisylvian areas usually involved in speech comprehension, plus the left ventral occipitotemporal cortex. When listening to normal speech, MK was subject to TTS and showed a larger difference between normal and reversed speech than controls in the left SMG, IFG, VWFA, precuneus, and SMA (green).

TTS, tickertape synesthesia; IFG, inferior frontal gyrus; SMG, supra-marginal gyrus; VWFA, visual word form area; SMA, supplementary motor area.

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We then compared MK to controls. In order to identify the functional correlates of TTS, we compared the contrast of normal minus reversed speech in MK relative to controls (Figure 2.1 and Table 2.1). MK's activation was stronger than in controls in a set of left-hemispheric regions: the IFG (MNI -33 5 26, Z=5.59; MNI -42 20 29, Z=5.02), the supramarginal gyrus (SMG; MNI -48 -43 32; Z=6.47), precuneus, the SMA, plus the fusiform gyrus close to the usual location of the VWFA (MNI -42 -46 -10; Z=4.25, corrected within an anatomically defined VOT region of interest; see Methods). We did not find differences between MK and controls in low-level visual cortex. For brevity, we will refer to this set of regions as the TTS network in subsequent results. We defined an anatomical mask including all language areas and the left VOT cortex (see Methods). The TTS network was almost entirely included in those regions (Supplementary Figure S2.1), in agreement with our first prediction.

Table 2.1. Experiment 1: Regions more activated in MK than in controls when listening to normal > reversed speech.

Region (left hemisphere)	Contrast	Peak coordinates (MNI)	Z value	Cluster size	p-value (cluster-level, FWE corrected)
SMG	MK > (G1 + G2)	-48 -43 32	6.47	61	0.005 *
	MK > G1	-48 -43 32	6.11	56	0.027 *
	MK > G2	-45 -40 29	5.3	75	<0.001 *
IFG	MK > (G1 + G2)	-33 5 26	5.59	117	<0.001 *
	MK > G1	-30 8 26	5.24	58	0.023 *
	MK > G2	-33 8 26	4.45	158	<0.001 *
IFG	MK > (G1 + G2)	-42 20 29	5.02		<0.001 *
	MK > G1	-42 20 29	5.6	34	0.148
	MK > G2	-42 20 29	3.92	158	<0.001 *
SMA	MK > (G1 + G2)	-3 -1 68	5.15	60	0.005 *
	MK > G1	-12 2 71	4.48	45	0.062

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	MK > G2	0 5 68	4.89	88	<0.001 *
Precuneus	MK > (G1 + G2)	-3 -55 59	4.64	42	0.03 *
	MK > G1	-3 -55 59	4	29	0.222
	MK > G2	-3 -52 62	4.65	232	<0.001 *
VWFA	MK > (G1 + G2)	-42 -46 -10	4.22	8	0.005 **
	MK > G1	-42 -49 -10	3.88	9	0.006 **
	MK > G2	-42 -46 -10	3.62	3	0.013 **

* Significant cluster-level P, with voxelwise $P < 0.001$ and clusterwise $P < 0.05$ corrected for multiple comparisons across the whole brain

** Significant cluster-level P, with voxelwise $P < 0.001$ and clusterwise $P < 0.05$ corrected for multiple comparisons within an a priori occipitotemporal region of interest (see Methods).

The five main regions displayed are the regions where MK showed overactivation when compared to all controls for the contrast normal speech > reverse speech.

In order to determine whether MK's over-activations were within the range of variation of control participants, we compared the contrast of normal minus reversed speech in each control subject minus all others. While 14 controls showed some significant differences from the group (excluding the cerebellum), those over-activations were randomly distributed all over the brain, with little overlap with the language and VOT masks (overlap range 0-58 voxels; mean = 11, as compared to MK's overlap of 232 voxels; Crawford t-test: $t(34)=11.2$; $p < 0.001$).

The two control groups G1 and G2 were scanned on different magnets, and G1 controls were younger than MK. In order to make sure that the overall differences which we observed between MK and controls were not due to age and scanner differences, we compared separately MK > G1 and MK > G2, and found that the main differences were remarkably replicated across both analyses, using the same statistical thresholds as in the global comparison (Figure S2.2). The MK > G1 comparison showed overactivation in the left SMG, IFG and VWFA. The MK > G2 comparison showed overactivation in the left SMG, IFG, SMA, precuneus and the VWFA (see Table 2.1). Moreover, we directly compared the two control groups. We found stronger activation for G1 > G2 in bilateral superior temporal sulci (STS),

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and stronger activation for G2 > G1 in the right prefrontal cortex (Figure S2.3). Those regions had no overlap with the areas distinguishing MK from controls.

Finally, the opposite contrast of normal minus reversed speech in all controls minus MK showed no activations. Activation by reversed speech minus rest and by normal speech minus rest did not differ between MK and controls.

In summary, this experiment supported our first prediction by showing abnormally strong activation during TTS, both in perisylvian frontoparietal language areas (the IFG and SMG), and in the left VOT at the usual location of the VWFA.

H. Experiment 2: Tickertape synesthesia as reverse reading

Beyond proposing that TTS should involve both the perisylvian and the VOT regions, we predicted that TTS-related activations should overlap with regions activated during word reading. Particularly, is the VOT component of the TTS network identical to the VWFA, as usually defined by word-specific visual activations? In order to delineate his reading network, MK was scanned while viewing images of words, faces, houses, tools, body parts, numbers, and during simple fixation (see Methods).

We first characterized the mosaic of VOT regions showing category preferences (Figure 2.2 and Table S2.2). MK had a fully normal pattern of specialization, as documented in a host of previous studies (see e.g. Deen et al., 2017; Malach et al., 2002; Monzalvo et al., 2012). Subtractions of each of the 3 categories words, faces and houses minus the other 2 showed the left VWFA (MNI -45 -52 -10; $Z > 8$), the right fusiform face area (FFA), and the bilateral parahippocampal place area (PPA), respectively. Subtractions of tools and of body parts minus the previous 3 categories showed bilateral lateral occipital cortex (LOC) activations.

Figure 2.2

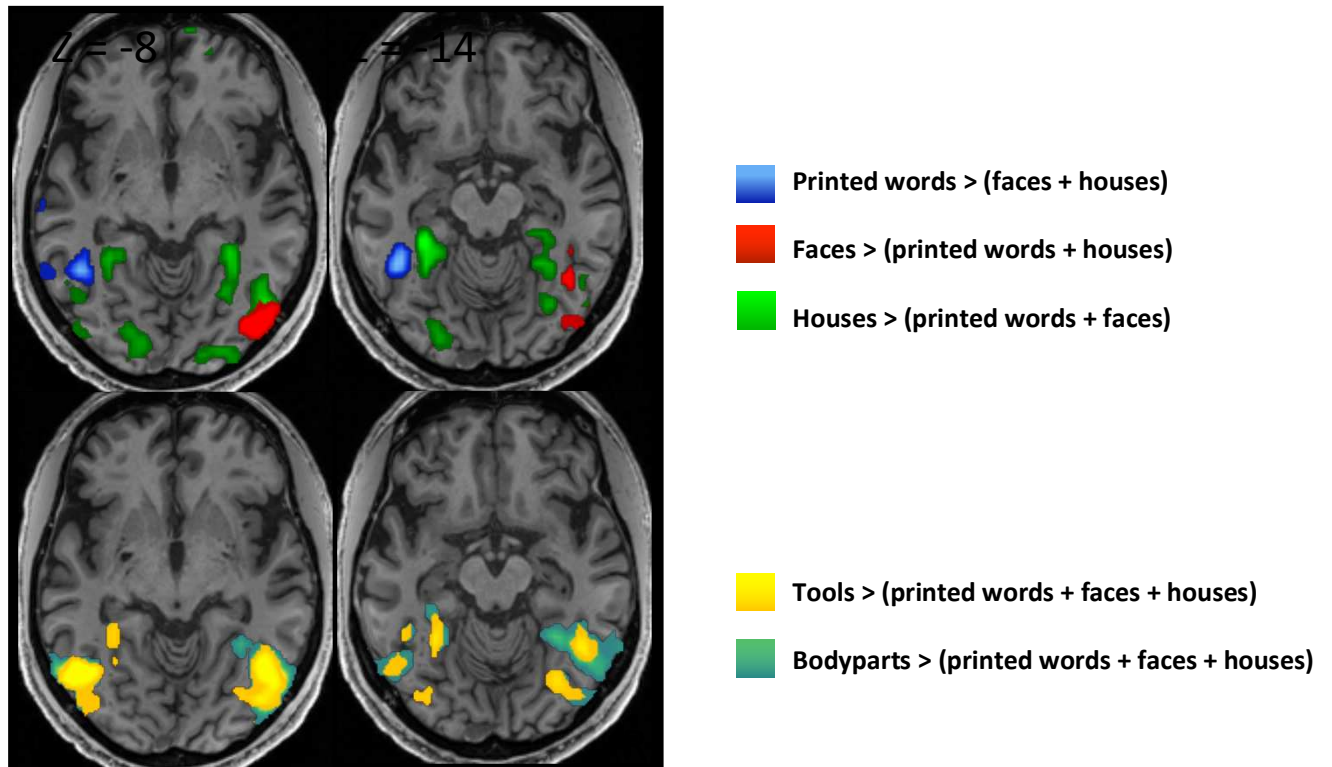


Figure 2.2. Experiment 2: Category-selective activations by visual objects. MK's VOT cortex showed a typical mosaic of category preference. Upper row : the VWFA for words (blue), the FFA and OFA for faces (red), the PPA for buildings (green). Bottom row : lateral occipital activations for tools (yellow) and body parts (blue-green).

VOT, ventral occipito-temporal; VWFA, visual word form area; FFA, fusiform face area; OFA, occipital face area; PPA, parahippocampal place area.

Crucially, the VOT area which was overactivated during TTS in Experiment 1 was identical to the VWFA defined here on the basis of visual stimulation (Figure 2.3A, white arrow). Beyond the VWFA, this overlap extended to all components of the TTS network (SMG, IFG, precuneus and SMA), which were also significantly activated here during reading (Figure 2.3A).

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Figure 2.3

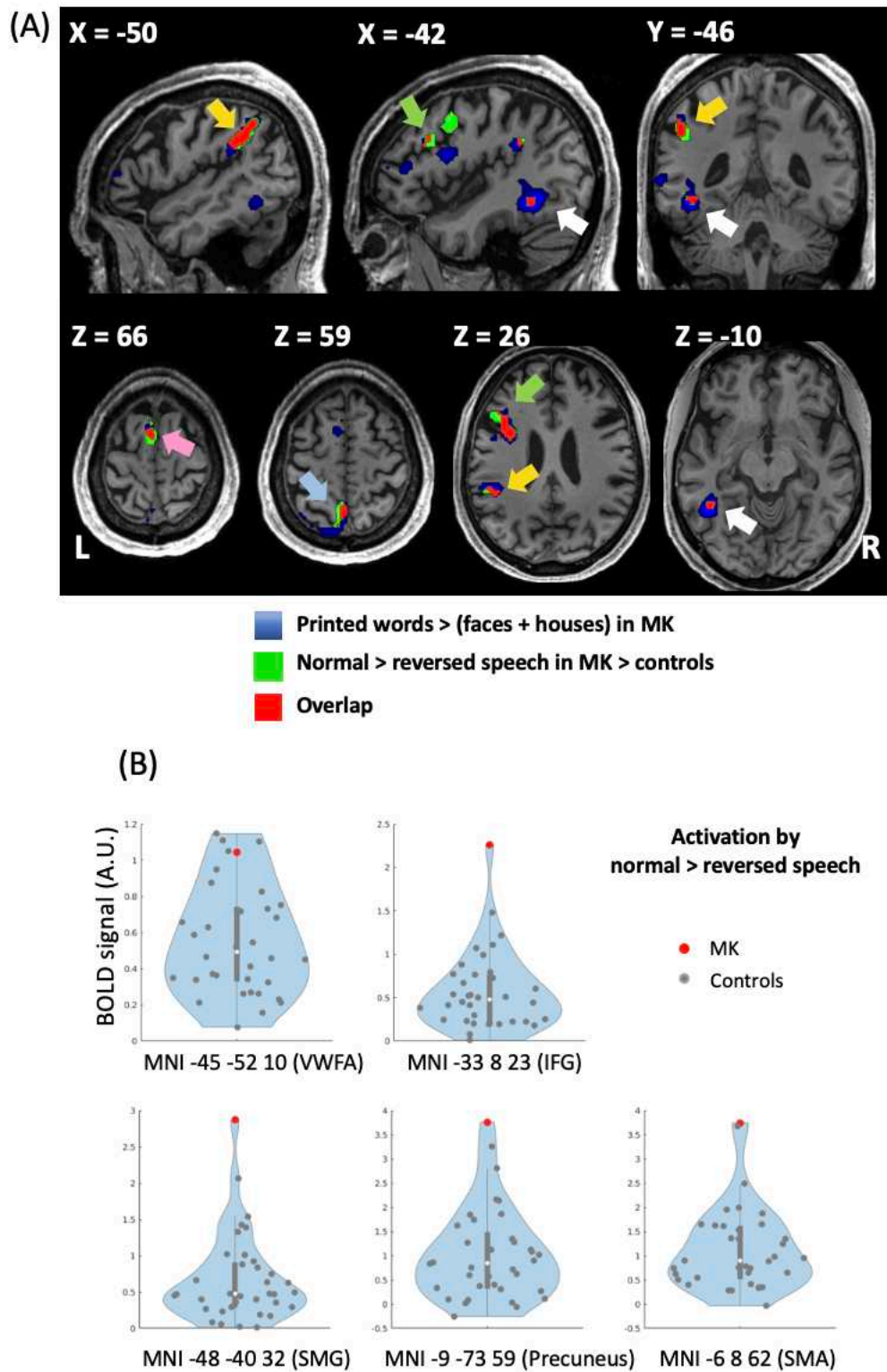


Figure 2.3. Experiments 1 and 2: Tickertape synesthesia (TTS) as inverted reading. (A) In MK, areas over-activated during TTS in Experiment 1 (green) and areas selectively activated

by printed words in Experiment 2 (blue) showed perfect overlap (red), in the VWFA (white arrow), SMG (yellow arrow), IFG (green arrow), SMA (pink arrow) and precuneus (light blue arrow). (B) Plot of individual activation intensity for the contrast of normal > reversed speech (Experiment 1), in MK (red dots) and controls (grey dots), at the peaks of MK's word-selective activations as identified in Experiment 2. In the IFG, SMG, precuneus and SMA, MK exceeded all of the 35 controls.

TTS, tickertape synesthesia; VWFA, visual word form area; IFG, inferior frontal gyrus; SMG, supra-marginal gyrus; SMA, supplementary motor area.`

Finally, in order to further compare MK to controls while avoiding statistical double dipping (Kriegeskorte et al., 2009), we defined ROIs of the TTS network on the basis of the current experiment, and plotted data from Experiment 1. In a 10 mm radius sphere centered on peaks of MK's activation by words minus faces and houses, we computed the average activation by the contrast of normal > reversed speech from Experiment 1, across the 10% most activated voxels (Figure 2.3B). In the SMG, IFG, precuneus and SMA, MK exceeded all of the 35 controls, with a significantly stronger activation (Crawford's t-tests: all $P_s \leq 0.001$) . At the VWFA, 4 controls showed higher activation than MK, who was marginally stronger than the group of controls ($p=0.055$).

In summary, we observed an extensive overlap of the activations related to TTS and to word reading, supporting our hypothesis that TTS resulted from an atypical operation of the cerebral reading system.

I. Experiment 3: Tickertape synesthesia for words and pseudowords

The reading system is thought to associate a phonological route mapping orthography to sounds on the basis of statistical regularities, and a lexico-semantic route mapping orthography to the mental lexicon, including stored word sounds. Assuming that TTS resulted from the reverse operation of the reading system, how did those two routes contribute to TTS? MK's introspection was that TTS was triggered by both real words, which appeared in

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their correct orthography, and by pseudowords, which appeared in a plausible spelling, suggesting that both reading routes were feeding the TTS phenomenon. The left SMG appeared as an obvious candidate for phonological processing, considering its involvement in a broad variety of phonological tasks, particularly whenever phonology has to be interfaced with orthography, audiovisual language, or sensorimotor processing (Binder, 2017; DeWitt and Rauschecker, 2012; Hickok and Poeppel, 2016; Martin et al., 2016; Pillay et al., 2014; Savill et al., 2019). The aim of Experiment 3 was to identify regions subtending lexical access from speech in MK, allowing us to then study their contribution to TTS. To this end, MK was scanned while he was presented with spoken words and with matched pseudowords. A group of controls were also scanned (see Methods).

As usual, both words and pseudowords triggered TTS. In MK, words and pseudowords activated essentially identical left-predominant fronto-temporo-parietal areas relative to rest. Those areas encompassed the entire TTS network, as identified in Experiment 1 (Supplementary Figure S2.4). Unless stated otherwise, all further analyses of this experiment were restricted to the volume which was activated in MK by averaged words and pseudowords > rest (voxelwise $p < 0.01$). We then compared MK minus controls for the contrasts words > rest and pseudowords > rest. Both comparisons replicated the results of Experiment 1, revealing overactivation in MK's TTS network, including the IFG, SMG and SMA (Supplementary Figure S2.5). The VWFA also was overactivated in MK for words > rest when correcting within the same a priori ROI as in Experiment 1.

We then compared activations by words and pseudowords, using univariate contrasts and multivariate pattern analysis (MVPA). The contrasts of words > pseudowords and pseudowords > words showed no significant effect of lexicality in MK. Controls showed stronger activation for pseudowords > words in bilateral superior temporal sulci and in bilateral inferior frontal gyri. MK did not differ from controls in either of those contrasts.

Moreover, we compared activation by words and pseudowords in MK at the peak voxels of the 5 regions of the TTS network as identified in Experiment 1. MK had stronger activations for pseudowords > words in the precuneus ($p < 0.001$), and no difference in the other regions (all $P_s > 0.07$).

We then used an MVPA searchlight to decode activation by words vs. pseudowords. In MK, the bilateral left-predominant posterior middle temporal gyrus (MTG) and the VWFA (MNI - 48 -46 -19) distinguished words from pseudowords better than chance (Figure 2.4). This pattern did not differ between MK and controls.

Figure 2.4

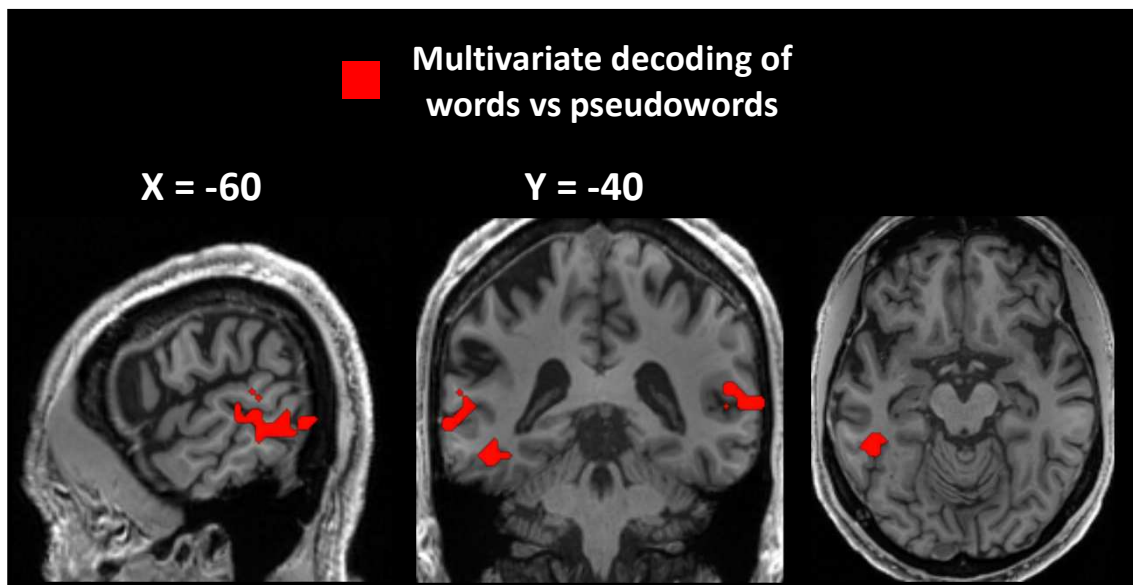


Figure 2.4. Experiment 3: Tickertape synesthesia (TTS) for words and pseudowords. MVPA discrimination between words and pseudowords in MK, showing effective decoding of lexical status in the left-predominant MTG and in the VWFA.

MVPA, multivariate-pattern analysis; MTG, middle temporal gyrus; VWFA, visual word form area.

In summary, while univariate analyses showed no significant effect of lexicality in MK, MVPA showed effective decoding in the VWFA, and in posterior MTG areas. Neuropsychology and imaging studies have long involved the left posterior MTG in lexical processing (see for instance Binder et al., 2009; Boatman, 2000; Davey et al., 2016; Hart and Gordon, 1990; Pillay et al., 2014), which makes it a sensible implementation of the lexical component of TTS. Having identified a set of candidate regions involved in all aspects of TTS, we are now in a position to investigate their functional interactions.

J. Dynamic causal modelling of tickertape synesthesia

The set of regions identified in Experiments 1-3 as associated to TTS generation belong to the usual cerebral reading network. This overlap was specifically demonstrated in Experiment 2 (Figure 2.3A). In addition to a higher univariate activation level in those regions, we predicted that TTS should be associated with an atypical flow of information among them, featuring an increase in top-down influences. We assessed this prediction using DCM, a method whose aim is to estimate the functional coupling among brain regions, and the changes in this coupling that are associated with different experimental conditions. Alternative models of how observed time series were generated in the brain are compared using a Bayesian approach (see Methods; Friston et al., 2003).

We modeled the causal links among the core regions involved in TTS generation, based on the hypothesis that speech perception triggers interacting phonological and lexical processes, eventually generating a vivid orthographic image. This is equivalent to assuming, as proposed before, that TTS results from the top-down operation of a two-route reading system. We re-analyzed MK's data from Experiments 1 and 3 using dynamical causal modeling (DCM), in order to identify the best model among alternative candidates. We translated our specific hypotheses into a set of constraints on the space of candidate models.

Among the regions identified in Experiments 1-3, we selected as regions of interest the mid-STG, the SMG, the MTG, and the VWFA (see Methods). To define the space of possible models, we assumed (1) that the mid-STG is the input region for all auditory stimuli, and that it is unidirectionally connected to the SMG, the MTG, or both (3 possible configurations); (2) that the VWFA is the output region subtending orthographic representations, and that it receives unidirectional input from the SMG, the MTG, or both (3 possible configurations); (3) that the SMG and MTG are mutually connected. Combining the 3 input and the 3 output options resulted in 9 families of models (Supplementary Figure S2.6) (Penny et al., 2010).

We then allowed some of the connections defining these families to be modulated by experimental factors. In Experiment 1, the connections from the mid-STG to the SMG and MTG could be modulated by the normal vs reversed speech factor. This is because this difference should only be relevant early in the flow of information, i.e. low-level acoustic stimuli should not propagate to high-level speech and language representations. In

Experiment 3, all connections could be modulated by the real words vs pseudowords factor (Supplementary Figure S2.6).

In summary, this resulted in 9 model families, including a total of 24 models for Experiment 1, and 256 models for Experiment 3.

For Experiment 1, the comparison of the 9 families selected a structure including all possible connections (posterior probability 0.86, Figure 2.5A). The second-best family did not include the connection from the SMG to the VWFA (posterior probability 0.11). For Experiment 3 also,

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the model featuring all possible connections was the most accurate (posterior probability 0.99, Figure 2.5B).

Figure 2.5.

Dynamic causal modelling of tickertape synesthesia

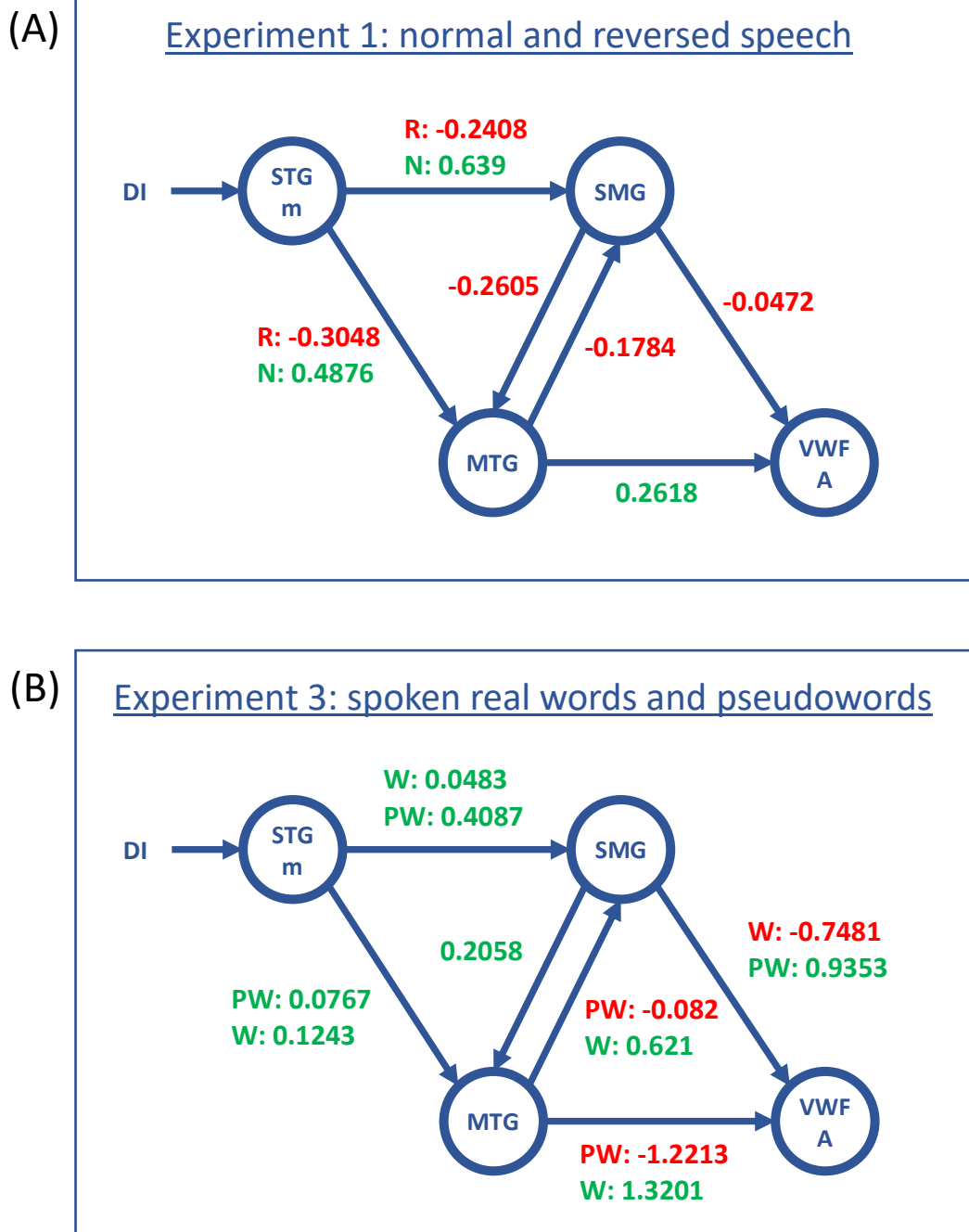


Figure 2.5. Dynamic causal modelling of tickertape synesthesia (TTS). Most likely models for MK's TTS-associated activations. The driving input (DI) corresponds to auditory stimulations

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entering the network through the STG. Blue arrows represent the intrinsic connections between the nodes. Values represent the strength of connections, which may be positive/excitatory (green) or negative/inhibitory (red). Two values are associated to connections significantly modulated by conditions, one value corresponding to each of the two experimental conditions. (A) In Experiment 1, normal speech (N) was driving the whole network down to the VWFA, while reversed speech (R) did not. (B) In Experiment 3, connections implementing the phonological route (STG-SMG and SMG-VWFA) were excitatory for pseudowords (PW) and inhibitory for real words (W). Conversely connections involved in the lexical route (MTG-VWFA and MTG-SMG) switched from inhibitory with pseudowords to excitatory with real words.

STG, superior temporal gyrus; SMG, supra-marginal gyrus; VWFA, visual word form area; MTG, middle temporal gyrus.

We then compared the models within the two winning families, in order to identify for each experiment the model with the most accurate pattern of modulation. In Experiment 1, the best model among 4 candidates had a posterior probability of 1. The connections from the STG to both the SMG and the MTG were significantly modulated, switching from strongly excitatory for normal speech to mildly inhibitory for reversed speech (Figure 2.5A). Regarding non-modulated connections, on average across normal and reversed speech, the links from the MTG to the VWFA were excitatory, while reciprocal connections between the SMG and MTG and connection from SMG to the VWFA were slightly inhibitory.

In Experiment 3, the best model among 64 candidates had a posterior probability of 0.31 (Figure 2.5B). Connections from the STG to both the SMG and MTG were excitatory for words and pseudowords. The connections implementing the phonological route, i.e. from the STG to the SMG and from the SMG to the VWFA, were both significantly modulated, both with an advantage for pseudowords over words. Particularly, the connection from to SMG to the VWFA switched from strongly excitatory for pseudowords to strongly inhibitory for words. Connections implementing the lexical route, i.e. from the STG to the MTG and from the MTG to both the VWFA and the SMG, were also modulated, all with an advantage for words over

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pseudowords. Particularly, the connection from the MTG to the VWFA switched from strongly excitatory for real words to strongly inhibitory for pseudowords. On average across words and pseudowords, the unmodulated connection (SMG to MTG) was excitatory (Figure 2.5B). The second-best model had a posterior probability of 0.28. The modulations were the same as in the best model, minus the one from the STG to MTG. Modulations for words and pseudowords on other connections were similar. The third best model had a posterior probability of 0.20. It was also similar to the best one, with an additional modulation of the SMG-to-MTG connection. Connections of the phonological route, i.e. from STG to SMG and from SMG to MTG, still showed an advantage for pseudowords (excitatory) over words (inhibitory). Thus the second- and third-best models preserved the main features of the dual-route pattern of connection, supporting the stability of our findings.

5. Discussion

A. Summary of findings

The main outcome of Experiment 1, in which we presented normal and reversed speech, was that a set of areas were more active in MK than in controls during normal than reversed speech, that is whenever MK was subject to synesthesia. Supporting our first prediction, this “TTS network” included both frontoparietal areas involved in speech processing and the VWFA subtending orthography (Figure 2.1).

In this experiment, one group of controls was not matched to MK in age, while the other group was scanned on a different device. It was therefore essential to determine whether the identification of the TTS network could not be confounded by differences in age or in scanning device. To this end, after delineating the TTS network by comparing MK vs all controls, we compared MK vs Group 1 and Group 2 separately. We observed a remarkable overlap between the outcome of both comparisons (Figure S2.1), demonstrating that MK’s activation peculiarities were uncontaminated by age or scanning device. Finally, we directly compared the two groups of controls, in order to determine whether potential differences would overlap with the TTS network. We only found minor differences, far remote from the TTS network, further confirming the robustness of our findings.

The differences which we found between the groups of controls were likely a correlate of aging (Figure S2.2). Indeed, like in the present case, older age is associated with increased prefrontal activation in a variety of tasks, including language tasks (for a review see Davis et al., 2014), an increase that correlates with improved speech discrimination (Du et al., 2016). Also like in the present case, older age is associated with weaker activation of auditory regions during speech perception (for a review see Cardin, 2016; Tremblay et al., 2013).

In Experiment 2, we delineated MK's reading areas by comparing activation by written words minus other categories of visual items. The set of reading-specific areas turned out to be essentially identical to the TTS network from Experiment 1, thus backing our second prediction that TTS and reading should rely on the same pathways (Figure 2.3). In Experiment 3, we refined our approach by presenting MK with spoken words and pseudowords. Both triggered TTS and activated the TTS network, although possibly with different underlying dynamics. This experiment allowed us to identify an MTG area involved in lexical reading, and presumably in the lexical component of TTS (Figure 2.4). Finally, we developed a dynamic two-route model of information flow during TTS. In MK, we found that speech was driving the TTS network, while reversed speech, which does not trigger synesthesia, had an inhibitory effect (Figure 2.5A). Moreover, functional connections implementing the phonological route were inhibitory when synesthesia was triggered by real words, while they were excitatory when synesthesia was triggered by pseudowords. The converse pattern prevailed for connections implementing the lexical route (Figure 2.5B). This result fits our fourth prediction that, analogous to reading processes, top-down information should follow distinct paths depending on whether synesthesia was triggered by words or pseudowords.

We will first discuss the two major components of TTS generation: The VWFA and its role in orthographic imagery, and the perisylvian areas and their role in translating speech to orthography.

A. The VWFA and orthographic mental imagery

We hypothesized that the orthographic content of TTS is supported by the VWFA, because there is ample evidence from brain damage and imaging that the VWFA computes orthographic representations from visual input. Importantly, in the absence of written stimuli, the VWFA may also be activated from top-down by speech (Cohen et al., 2021; Ludersdorfer

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et al., 2016; Yoncheva et al., 2010). We reasoned that such top-down effects may contribute to orthographic imagery, and that TTS may be seen as an exceptionally vivid and automatic form of such imagery, an ability possessed to some degree by all literate individuals (Bourlon et al., 2009; Holm et al., 2015). Supporting the role of the VWFA in orthographic imagery, at least some of the alexic patients with VWFA lesions lose this type of imagery (Bartolomeo et al., 2002; Rosazza et al., 2007; Sirigu and Duhamel, 2001; Volpato et al., 2012). This fits with the present findings that the VWFA was involved in TTS: the VOT region which was over-activated during TTS, and the VWFA as defined by its preference for written words, were precisely identical.

In MK, TTS largely escaped voluntary control, while mental imagery is usually optional and effortful (Mazard et al., 2002). However the degree of automaticity of orthographic imagery is variable across individuals, rather than distributed in an all-or-none manner between TTS and non-TTS individuals. Thus, Holm et al. (2015) asked participants from a general population to specify the extent of their control of word visualization. A small number of subjects qualified for TTS in the strictest sense, similar to MK, synesthesia being obligatory, and induced by other persons' speech, one's own speech, and when thinking verbally. Interestingly, a larger number of participants reported that word visualization was under some voluntary control, relevant to the issue of continuity between synesthesia and normal perception, a controversial issue in the field of synesthesia studies (Deroy and Spence, 2016; Martino and Marks, 2001).

Considering the vividness and automaticity of mental imagery in MK, we may draw a parallel between TTS and the visual hallucinations that occur in schizophrenia, in Parkinson's disease and other neurological conditions, and in the Charles Bonnet syndrome. Although the mechanisms of such hallucinations are still elusive, they are often associated with overactivation of visual cortices, which show abnormal intrinsic and distant connectivity, supporting predominant top-down over bottom-up influences on visual experience (Amad et al., 2014; Dujardin et al., 2020; ffytche et al., 1998; Hahamy et al., 2021; Waters et al., 2014).

B. From speech to orthography

The superior temporal gyrus. In the dynamical model of TTS, we treated the mid-STG cortex as a common auditory input region, because it was equally activated by both speech and reversed speech. Indeed the center of the STG region of interest (MNI -48 -16 5) belonged to

the early auditory cortex, as defined architectonically, with a probability of 85% (areas TE 1.0 1.1 1.2) (areas TE 1.0 1.1 1.2; Morosan et al., 2001). Further supporting the role of the mid-STG as the initial stage of TTS generation, DCM showed that it was significantly driving the SMG and MTG whenever MK was subject to synesthesia.

In MK, both externally perceived and inner-speech triggered synesthesia. This may result from the remarkable overlap of STG activation by external and by inner-speech (Alderson-Day et al., 2016; Alderson-Day and Fernyhough, 2015; Shergill et al., 2002), and also during auditory-verbal hallucinations in schizophrenia patients (Jardri et al., 2011).

The supramarginal gyrus. Beyond the auditory entry point, the STG is a complex mosaic of modules computing various representations of speech and sounds (Binder, 2015; DeWitt and Rauschecker, 2012; Scott, 2019; Yi et al., 2019). In continuity with the posterior STG, the SMG supports phonological representations at the interface with other modalities. This includes audio-motor mapping for speech production (Hickok and Poeppel, 2015), phonological working memory (Buchsbaum et al., 2005b; Buchsbaum and D'Esposito, 2008), lip-reading and audiovisual language (e.g. Dick et al., 2010; Hocking and Price, 2008; Wright, 2003).

It is also critically involved in non-lexical reading, such that per-operative stimulation of the SMG disrupts selectively the reading of pseudowords but not of exception words (Roux et al., 2012; Simos et al., 2000). Similarly, transcranial stimulation of the SMG interferes with sound-oriented but not with meaning-oriented reading (Pattamadilok et al., 2010; M. W. Sliwinska et al., 2015). Further supporting its role in phoneme-grapheme correspondences, the SMG is more activated by pseudowords than real words, both during reading (J. S. Taylor et al., 2013) and during spelling (DeMarco et al., 2017). Graves & Binder (2010) found that the left SMG showed a negative effect of bigram frequency, millimeters away from the current SMG peak, revealing sensitivity to the difficulty in binding phonemes and graphemes. Moreover Bouhali et al. (2019) found stronger functional connectivity of the SMG with the VWFA when reading aloud pseudowords than during lexical decision with words, that is whenever phonological demands were higher.

In MK, the role of the SMG in TTS may be to map perceived phonemes to illusory graphemes on the basis of statistical regularities, in interaction with the lexical route. One may putatively view the overactivation of the SMG in synesthesia as functionally symmetric to the

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hypoactivation observed repeatedly in developmental dyslexia, where phoneme-grapheme mapping is impaired (D’Mello and Gabrieli, 2018; Kronbichler et al., 2006).

The middle temporal gyrus. The posterior MTG is one of the most systematically activated regions during lexico-semantic tasks (Binder et al., 2009), and electrical stimulations cause transcortical sensory aphasia, that is an impairment of language comprehension with preserved phonological processing (Boatman, 2000), in agreement with the consequences of focal lesions (Hart and Gordon, 1990). This region may be seen as a “convergence hub” for binding spread-out pieces of lexical knowledge (Patterson et al., 2007), or similarly as a “semantic control” region (Davey et al., 2016, 2015; Jedidi et al., 2021).

During reading, the posterior MTG is also consistently activated when contrasting words minus pseudowords (for meta-analyses see McNorgan et al., 2015; J. S. Taylor et al., 2013), supporting its involvement in the lexical reading route (Binder et al., 2003). However, lexicality interacts with task, such that MTG activation is mostly present during tasks with strong lexical demands, typically lexical decision relative to reading aloud (McNorgan et al., 2015). This may explain why in Experiment 3, where participants only had to detect an odd-ball meaningless signal, we found no univariate effect of lexicality. In the MTG, MVPA proved more sensitive for discriminating words from pseudowords, similar to previous findings (Baeck et al., 2015; Fedorenko et al., 2012; Mattheiss et al., 2018).

This background made the MTG, as identified in MK during synesthesia, a sensible implementation of lexical processing within a simple model of TTS.

After discussing the putative roles of the VWFA and perisylvian areas in TTS, we now turn to the dynamic model of their interactions which we explored using DCM.

C. A simple dynamic model of TTS

Constraints on the model. When designing the DCM model of synesthesia, we selected a set of 4 areas of interest, admittedly a simplistic network, leaving aside the IFG, SMA and precuneus, although they were also over-activated in MK. This allowed us to restrict the space of possible models on the basis of strong a priori motivations, a methodological requirement of DCM (Stephan et al., 2010). The STG, SMG, MTG, and VWFA are essential components of auditory, phonological, lexical, and orthographic processing, respectively, and were all defined

on the basis of their functional features during TTS. The 4 selected regions thus provided a sensible sampling of the lexical and phonological routes.

We reasoned that the IFG and SMA probably played no critical role in the generation of TTS. While the IFG is often activated by reading words and pseudowords (e.g. F. Bouhali et al., 2019; Heim et al., 2005), it is thought to control spoken phonological output, and should not contribute to the purely audio-visual phenomenon of TTS (J. S. Taylor et al., 2013). The SMA is also commonly activated during reading, and its primary language-related role is thought to be the control of speech output (Alario et al., 2006; Hertrich et al., 2016). Finally, the precuneus is a top-level hub in the hierarchy of brain areas, it intervenes in a variety of cognitive control processes, and its putative role in TTS is difficult to pinpoint from the current data (Cavanna and Trimble, 2006; van den Heuvel and Sporns, 2013). Still in a recent meta-analysis, Spagna et al. (2021) proposed that activation of both the SMA and precuneus are associated with mental imagery, and their putative role in TTS may deserve further study.

In defining the space of possible models, we posited that the SMG and MTG, as implementing the phonological and lexical routes, should always have the possibility of influencing each other. There is a host of behavioral evidence of close interactions between the two routes. Thus, illustrating the automatic impact of phonology on lexical reading, during visual lexical decision, words are automatically parsed into phonologically defined syllables (Conrad et al., 2007). In the same task, response to word targets is facilitated by pseudoword homophone primes (mayd MADE), as compared to control primes (mard MADE), revealing the computation of phonological codes and their impact on word reading (Grainger and Holcomb, 2008). Conversely, showing the influence of lexical knowledge on phonological reading, pseudowords are pronounced faster when they are orthographically similar to a large number of real words (Peereman and Content, 1995). A point of interest in the context of TTS as “inverted reading”, not only the reading but also the spelling of pseudowords is also influenced by the existence and frequency of real word neighbors (Tainturier, 2013).

At the brain level, close interactions between the SMG and posterior MTG are supported by their strong anatomical connections (Caspers, 2011; Jung et al., 2017; Xu et al., 2016) and their functional connectivity at rest (Turken and Dronkers, 2011; Xu et al., 2016).

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Architecture and modulations of the TTS network. In Experiment 1, normal speech had a strong excitatory driving influence on the circuit, while reversed speech had a minor inhibitory effect. Moreover, in the most likely model family, words propagated from the STG to both the MTG and SMG, while only the latter further relayed information to the VWFA. In other terms, until they are assigned an orthographic form by the VWFA, perceived words mostly follow the lexical route through the MTG. The specific contribution of the MTG here may be to allow access to stored orthographic knowledge, possibly by performing semantic disambiguation of auditory words (Davey et al., 2016, 2015; Jedidi et al., 2021; Patterson et al., 2007). Finally, the phonological route (SMG) only had a small inhibitory effect on the lexical route (MTG), suggesting that it did not play an important role in generating TTS for normal speech.

This interpretation is aligned with the DCM results of Experiment 3 which, in contrast to Experiment 1, included both normal speech (real words) and pseudowords. The most likely network included the same connections as in Experiment 1. When first neglecting inhibitory effects, Experiment 3 essentially recapitulates Experiment 1, in that real words reach the VWFA through the lexical route, i.e. through the MTG. In contrast, pseudowords drive the VWFA through the phonological route, i.e. through the SMG. The pattern of inhibitory effects further suggests that the lexical route (MTG to VWFA) acts to lessen VWFA responses to pseudowords, whereas the phonological route (SMG to VWA) dampens VWFA responses to real words. This indicates that the two routes are somehow competing for access to the VWFA, eventually facilitating accurate orthographic coding of both words and pseudowords. Overall, these results support our fourth hypothesis that top-down influences should follow distinct lexical vs phonological paths depending on whether synesthesia is triggered by words or pseudowords.

In Experiment 3, we found only a weak excitatory effect of real words from the STG to the SMG, while in Experiment 1 the excitatory effect of normal speech was strong. As real words consist in normal speech, we may have expected a strong positive effect of words in Experiment 3 also. Leaving aside DCM reproducibility issues, this discrepancy may result from differences in task requirements: In Experiment 1, participants payed attention to a meaningful narration while in Experiment 3, they were encouraged to process words at a low level. Words lists carried no sentential meaning, and the target “tatatata” could be best detected by paying attention to phonology. This may explain why words had a stronger

influence in Experiment 1 than 3. Direct comparisons of words, pseudowords and low-level sounds with a constant task could clarify this issue.

Schematically, we construed TTS as an idiosyncratic operation of the reading system. We will now briefly discuss the alternative view of TTS as inner spelling.

D. TTS as inner spelling

We proposed that TTS resulted from intense top-down activation of the reading network, initially because MK reported a subjective experience of inner reading, with no active spelling-related feeling. Alternatively however, TTS could have been construed as an extreme form of inner spelling. In some sense MK was automatically “writing out in his head” the speech he was perceiving. Actually those two points of view are largely equivalent, as writing and spelling share core cognitive components and neural substrates (for reviews see Purcell et al., 2017; Rapp and Dufor, 2011). There is thus a shared set of perisylvian regions whose lesion yields both reading and spelling deficits (Philipose et al., 2007).

Focusing on regions which are presumably involved in MK’s synesthesia, the left IFG and the VWFA are activated by both reading and spelling, show cross-task adaptation suggestive of shared orthographic representations (Ellenblum et al., 2019; Purcell et al., 2017, 2011), and are both sensitive to word frequency during spelling and reading (Graves et al., 2010; Rapp and Dufor, 2011). The left SMG, posterior MTG, precuneus and SMA are also activated during both reading and spelling (DeMarco et al., 2017; Rapp and Dufor, 2011). Moreover, the SMG plays a predominantly phonological role during spelling, as it does during reading and in TTS (DeMarco et al., 2017). Thus, TTS may reflect atypical functioning, during speech perception, of the single network which links sounds and letters during both reading and writing.

E. Ticker tape synesthesia and brain connectivity

Beyond TTS, atypical anatomical or functional connectivity is at the core of most theories of synesthesias (for a recent review see Ward and Simner, 2020). Within this broad framework, theories differ along multiple dimensions: is there an increase in anatomical or in functional connections, are those disinhibited or structurally stronger (Grossenbacher and Lovelace, 2001), do they link the inducer and concurrent regions directly or through higher-level cortices (Hubbard et al., 2011; van Leeuwen et al., 2011), do the same principles apply to all forms of

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synesthesias, etc? For instance, in grapheme-color synesthesia, the most studied type of synesthesia, increased fractional anisotropy was detected in the fusiform and other regions (Rouw and Scholte, 2007). Furthermore, differences in functional connectivity were found between synesthetes and controls (Sinke et al., 2012), and between subtypes of grapheme-color synesthetes (van Leeuwen et al., 2011). However the reproducibility of those findings across studies appears questionable (Hupé and Dojat, 2015). Our DCM analysis clarifies the pattern of functional connectivity involved in TTS, but is not in a position to adjudicate between general theories of synesthesia.

Of particular interest is the idea that synesthesia “magnifies connections present in early life that are pruned and/or inhibited during development and that persist in muted form in all adults” (Spector and Maurer, 2009). In this hypothesis, TTS would reflect the persistence of a transient state of stronger connection which would normally vanish after literacy acquisition. Indeed, in a longitudinal study of reading acquisition, Dehaene-Lambertz et al. (2018) observed an increase in word-specific activation in parietal (MNI -44 -42 46) and frontal (MNI -48 6 24) areas during the first year of alphabetization, only millimeters away from MK’s SMG and IFG overactivation peaks. These two regions later show a decrease in activation, and are thought to play a transient role in reading acquisition, specifically in binding phonemes and graphemes. One may thus speculate that long-term survival of a normally transient role of the SMG and IFG, contributes to the genesis of TTS.

Furthermore, it is also possible that TTS involves the persistence of processes linked to spelling rather than reading acquisition. Indeed effective mental imagery in children does not predict better reading acquisition, while it predicts spelling acquisition (Guarnera et al., 2019). During spelling, it is necessary to generate and maintain an orthographic representation of the current word while serially writing or typing the component letters (Buchwald and Rapp, 2004). This orthographic working memory, or “graphemic buffer”, may involve strings of abstract letters, but also visual images of the current string, providing a target pattern and allowing for feedback control during the writing process. Visual control plays a limited role in expert writers (Danna and Velay, 2015), but it is critical during handwriting learning (Meulenbroek and Van Galen, 1988). Thus TTS might be construed as the persistence of an hyperactive graphemic buffer and its associated visual images. Indeed the maximum overlap of lesions yielding graphemic buffer impairments is millimeters away from MK’s SMG over-

activation (Rapp et al., 2016), while the VWFA would support mental images per se as discussed before.

As a final topic for speculation related to the developmental origins of TTS, one may mention the intriguing case of a man in whom TTS was associated with two other developmental conditions, chronic psychosis and an arachnoid cyst (Bastiampillai et al., 2014).

6. Conclusion

Among the many kinds of synesthesia, as many as 88% involve language either as the “inducer” as in grapheme-color synesthesia, or as the “concurrent” as in perfect pitch (Simner, 2007; Simner et al., 2006). TTS stands out as the single form of synesthesia in which both the inducer and the concurrent are language representations. Specifically, TTS involves the same orthographic and phonological representations which support reading and spelling. One may thus speculate that TTS results from an atypical developmental trajectory with enduring hyperconnectivity between speech and vision, a situation in some sense symmetrical to developmental dyslexia, in which defective connectivity was repeatedly observed (e.g. Cui et al., 2016; Schurz et al., 2015; Van Der Mark et al., 2011).

At this stage, the present study being restricted to a single case, and in the absence of any previous data on the cerebral mechanisms of TTS, all general inferences should be cautious. Francis Galton (1883) noted that “the experiences differ in detail as to size and kind of type, colour of paper, and so forth, but are always the same in the same person”, pointing to the issue of individual variability. Beyond the perceptual features of TTS mentioned by Galton, synesthetes also differ in the level of control that they exert on TTS, and in the stimuli (external speech, inner speech, etc) that trigger the phenomenon (Holm et al., 2015). We predict that all cases of TTS should conform to the general pattern of “upended reading”, but expect that the exact pattern of visual activation, and the involvement of attention and control systems should vary substantially.

Further study of TTS may therefore shed light on the mechanisms of reading acquisition, their variability and their disorders. Among others, future studies should address resting-state and anatomical connectivity in TTS individuals, potential behavioral differences in oral and written language processing between TTS individuals and controls, associations with other

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synesthesias, variants and dissociations within TTS, and TTS-like phenomena in typical and dyslexic children learning to read.

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We here report a single-case neuroimaging of one tickertaper, and we also had some description of his subjective perception. In order to continue the work of Chun and Hupé (2013) and Holm et al. (2015), to better characterize what is happening during TTS, our second study was centered on phenomenological description of TTS.

CHAPTER III

Tickertape synesthesia: Phenomenology

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Exploratory Report

Subtitled speech: Phenomenology of tickertape synesthesia

Fabien Hauw^{a,b,*}, Mohamed El Soudany^a and Laurent Cohen^{a,b}^a Inserm U 1127, CNRS UMR 7225, Sorbonne Universités, Institut du Cerveau, ICM, Paris, France^b AP-HP, Hôpital de La Pitié Salpêtrière, Fédération de Neurologie, Paris, France

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ABSTRACT

With effort, most literate persons can conjure more or less vague visual mental images of the written form of words they are hearing, an ability afforded by the links between sounds, meaning, and letters. However, as first reported by Francis Galton, persons with ticker-tape synesthesia (TTS) automatically perceive in their mind's eye accurate and vivid images of the written form of all utterances which they are hearing. We propose that TTS results from an atypical setup of the brain reading system, with an increased top-down influence of phonology on orthography. As a first descriptive step towards a deeper understanding of TTS, we identified 26 persons with TTS. Participants had to answer to a questionnaire aiming to describe the phenomenology of TTS along multiple dimensions, including visual and temporal features, triggering stimuli, voluntary control, interference with language processing, etc. We also assessed the synesthetic percepts elicited experimentally by auditory stimuli such as non-speech sounds, pseudowords, and words with various types of correspondence between sounds and letters. We discuss the potential cerebral substrates of those features, argue that TTS may provide a unique window in the mechanisms of written language processing and acquisition, and propose an agenda for future research.

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1. Introduction

Literate persons with the ability to form mental images, can voluntarily conjure visual images of words they are hearing, an ability afforded by the links between sounds, meaning, and letters which actually define literacy. Such images are vague and their generation requires substantial effort.

However, as first reported by Francis Galton, “some few persons see mentally in print every word that is uttered (...) and they read them off usually as from a long imaginary strip of paper, such as is unwound from telegraphic instruments” (Galton, 1883). Galton noted that beyond this core subjective phenomenon, “the experiences differ in detail as to size and kind of type, color of paper, and so forth, but are always the same in the same person”. For instance, the botanist George

* Corresponding author. Inserm U 1127, CNRS UMR 7225, Sorbonne Universités, Institut du Cerveau, ICM, Paris, France.

E-mail address: fabien.hauw@orange.fr (F. Hauw).

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Subtitled speech: Phenomenology of tickertape synesthesia

Fabien Hauw^{a, b}, Mohamed El Soudany^a, Laurent Cohen^{a, b}

a. Inserm U 1127, CNRS UMR 7225, Sorbonne Universités, Institut du Cerveau, ICM, Paris, France

b. AP-HP, Hôpital de La Pitié Salpêtrière, Fédération de Neurologie, Paris, France

1. Abstract

With effort, most literate persons can conjure more or less vague visual mental images of the written form of words they are hearing, an ability afforded by the links between sounds, meaning, and letters. However, as first reported by Francis Galton, persons with tickertape synesthesia (TTS) automatically perceive in their mind's eye accurate and vivid images of the written form of all utterances which they are hearing. We propose that TTS results from an atypical setup of the brain reading system, with an increased top-down influence of phonology on orthography. As a first descriptive step towards a deeper understanding of TTS, we identified 26 persons with TTS. Participants had to answer to a questionnaire aiming to describe the phenomenology of TTS along multiple dimensions, including visual and temporal features, triggering stimuli, voluntary control, interference with language processing, etc. We also assessed the synesthetic percepts elicited experimentally by auditory stimuli such as non-speech sounds, pseudowords, and words with various types of correspondence between sounds and letters. We discuss the potential cerebral substrates of those features, argue that TTS may provide a unique window in the mechanisms of written language processing and acquisition, and propose an agenda for future research.

2. Introduction

Literate persons with the ability to form mental images, can voluntarily conjure visual images of words they are hearing, an ability afforded by the links between sounds, meaning, and letters which actually define literacy. Such images are vague and their generation requires substantial effort. However, as first reported by Francis Galton, “some few persons see mentally in print every word that is uttered (...) and they read them off usually as from a long imaginary strip of paper, such as is unwound from telegraphic instruments” (Galton, 1883). Galton noted that beyond this core subjective phenomenon, “the experiences differ in detail as to size and kind of type, colour of paper, and so forth, but are always the same in the same person”. For instance, the botanist George Henslow reported that the illusory words displayed “extreme restlessness” and that they “oscillated, rotated, and changed”. Galton also briefly discussed the involvement of attention, indicating that some individuals “attend to the visual equivalent and not to the sound of the words”, sometimes resulting in actual embarrassment, as reported by a fellow member of the Royal Society who told Galton that he “often craved for an absence of visual perceptions, they are so brilliant and persistent”.

Ever since this initial description, this phenomenon was subsumed under the broad label of synesthesias, a family of perceptual peculiarities, in which stimulation in one sensory or cognitive domain automatically induces an unusual and vivid perception in a distinct sensory or cognitive domain. Two instances of synesthesia which have received much attention are grapheme-color synesthesia, in which digits and letters, printed or even imagined, are perceived as colored, and sound-colour synesthesia, in which the perception of a musical sound evokes the experience of color. The illusory perception of written words during speech perception was labelled “ticker tape synesthesia” (TTS), to which we will stick for consistency, although “subtitles synesthesia” would be a more readily understandable term.

Beyond being casually mentioned among the more than 100 types of synesthesia, TTS has received little scientific attention. Chun and Hupé (2013) estimated the prevalence of TTS at 7%, a likely overestimation due to sampling biases. They also noted that TTS is often associated with other types of synesthesia. Holm et al. (2015), over several samples of population, found 1.4% of “obligatory” tickertapers who experienced TTS unwillingly

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whenever hearing external speech or their own voice, or even when thinking in words. The rate rose to 8.7% for individuals in whom some orthographic imagery occurred only occasionally. Overall, a maximum incidence of a few percent would be in the range of other types of synesthesia (Johnson et al., 2013; Rothen and Meier, 2010; Simner et al., 2006). Although TTS has no significant impact on everyday life, Coltheart and Glick (1974) documented an advantage in spelling words backward, a task that may be facilitated by the use of a stable mental image of written words.

TTS stands out of the list of known synesthesias because, in synesthesia parlance, both the inducer (speech) and the concurrent (orthographic image) are language representations. We therefore propose that the potential interest of TTS goes far beyond the anecdote, as it may provide a unique window in the mechanisms of written language processing and acquisition.

In the brain of literate persons only, words are coded as series of letters, and dedicated processes allow for the translation from orthography to sound and meaning during reading, and for the opposite translation during spelling. Those novel features develop during the acquisition of reading, through delicate changes in visual and language areas of the brain, and changes in their connectivity (Dehaene et al., 2015; Dehaene-Lambertz et al., 2018). This complex tuning occurs under a variety of environmental and genetic constraints, resulting in substantial individual variability in eventual performance level. For instance, twin studies have shown significant heritability of reading abilities (Nunn et al., 2002), while factors such as birth weight represent risk factors for reading disorders (Mascheretti et al., 2018). At one end of the performance spectrum stand the various types of developmental dyslexia (Friedmann and Coltheart, 2018), associated with atypical anatomical and functional brain features (Norton et al., 2015; Ramus et al., 2018). TTS should be understood, on this background, as a further form of atypical setup of the cerebral literacy system.

In a recent study we assessed the hypothesis, first put forward by Holm (Holm et al., 2015), that TTS would result from unusually intense top-down influences from phonological and lexical representations, embodied in left perisylvian language areas, onto orthographic codes subtended by the left ventral occipitotemporal cortex (Hauw et al., 2023c). Using fMRI in a single tickertaper, we showed that a set of left-hemispheric areas were more active in the tickertaper than in controls during the perception of normal than reversed speech, including

perisylvian areas involved in speech processing, and the Visual Word Form Area, a left occipitotemporal region subtending orthography. Those areas were identical to those involved in reading, supporting the construal of TTS as “upended reading”. Using dynamic causal modeling, we further showed that TTS indeed relied on increased top-down flow of information.

Here, as a first step towards a broader understanding of TTS, we endeavored to draw a fuller portrait of its core features and of its variations along the multiple dimensions conjectured by Galton, including visual and temporal features, triggering stimuli, voluntary control, interference with language processing, etc. We do so based on an extensive questionnaire, and on the description of synesthetic percepts elicited by auditory stimuli such as non-speech sounds, pseudowords, and words with various types of correspondence between sounds and letters. We discuss the potential cerebral substrates of those features, and propose an agenda for future research.

3. Methods

A. Recruitment of participants

We created a short description of what TTS is, and recruited participants by broadcasting it through email and social networks, targeting particularly groups of students and university members, and groups devoted to synesthesia, psychology, and neuroscience. Among individuals who answered us, we included those who reported having TTS, were over 18 years old, and had no neurologic or psychiatric history. Participants provided written informed consent and the study was approved by the institutional review board of the INSERM (protocol C13-41). We proposed to all participants (i) a questionnaire mostly aiming at characterizing the subjective features of TTS, and (ii) a series of auditory stimuli for which they were asked to report the content of the elicited synesthesia. No objective tests were available to ensure that all self-reported synesthetes actually had TTS, contrary to other synesthesias in which it is at least possible to assess the consistency of induced-concurrent associations, for example in grapheme-colour synesthesia (Carmichael et al., 2015).

B. Questionnaire on ticker tape synesthesia

The full content of the questionnaire is reported as supplementary material. The survey addressed the following topics.

i. Demographics

Participants were asked about their gender, age, profession, native language, education level, reading proficiency, handedness, potential auditory or visual impairments, learning disabilities. We asked them to report their associated synesthesias if any, including : space-time (the experience of time as a spatial construct), sound-color (involuntary experience of colors when hearing sounds), number-space (ordinal sequences such as numbers map to stable spatial locations in mental space), grapheme-color (associations between letter and colors), digit-color (associations between digits and colors), ordinal-linguistic (ordinal sequences such as numbers or days, have personalities, emotions or gender), auditive-gustatory (experience of tastes that are triggered by the perception of non-taste related words), and perfect pitch. They were also asked about TTS and other synesthesias among family members.

ii. Subjective features of TTS

We investigated the following dimensions of TTS experience (see supplementary material for full details).

Onset and awareness of TTS: TTS being a developmental phenomenon, the first questions aimed at determining when the synesthesia emerged, and when and how participants realized it was uncommon.

Stimuli that trigger and modulate synesthesia: On a rough definition, TTS is triggered by speech. In order to determine the detailed features of speech actually triggering and modulating TTS, we asked the following questions. Is synesthesia triggered by external speech, by one's own speech, etc? Do auditory parameters such as emotional content or gender of the speaker modulate TTS perception? What extent of voluntary control do participants have over the phenomenon?

Visual features: The very substance of TTS being mental visual images of unusual vividness, we asked the following to characterize the features of images as precisely as possible. Do

participants perceive the subtitles within their own mind or projected in the external world? Are subtitles always perceived in the same place? Are they written in upper- or lower-cases, are they colored, etc? How many words are perceived at the same time? How are number words perceived?

Temporal features: Although actual mental chronometry may be out of the reach of introspective reports, we tried to identify the gross relative temporal unfolding of the auditory and visual components of TTS, asking the following questions. Is there any delay between speech perception and the onset of synesthesia, and do subtitles persist for some time after speech stops?

Non-word triggers of TTS: To the above exploration of the main triggers of TTS, we added a set of questions addressing stimuli at the edge between speech and non-speech. Is TTS triggered by utterances in a foreign language, by novel words, by different classes of non-speech sounds such as sneezing, meowing, or the sound of a bell?

Interference with daily life: Finally, in an attempt at identifying objective markers of TTS, we asked whether participants found any advantage or disadvantage to TTS in their daily life. For instance, we tried to determine what happens when reading a book near someone speaking, or when watching a movie with subtitles.

C. Assessment of TTS with auditory stimuli

Participants were presented with auditory stimuli, and were asked to write down whatever subtitles they may induce. They could replay each sound as often as wished. We used the following types of sounds.

i. Non-speech stimuli

We selected audio files from an open sound library (www.lasonotheque.org), including (1) animals sounds (meowing, bleating, barking and crowing), (2) human noises (laugh, cough, yawning and sneezing), (3) sounds of inanimate objects (car engine, ring tone, iron bar falling, gunshot), and (4) short wordless musical tunes.

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ii. Words with exception spelling

Exception words do not obey usual phoneme-to-grapheme correspondences, and spelling them out therefore requires access to stored lexical knowledge of orthography (e.g. YACHT or OIGNON in French). By presenting TTS individuals with exception words, we wished to determine whether such lexical knowledge was reflected in the content of subtitles. We selected 10 French exception words that had at least 3 phonemes, and generated the corresponding audio files using the ttsreader.com speech generation software.

iii. Homophone words

Homophone words share the same pronunciation but differ in meaning. When they also differ in orthography they are called non-homographs (e.g. LEAK vs LEEK, or CONTE vs COMPTE in French). By presenting such words in spoken form, we wished to determine whether subtitles featured only a single spelling, possibly the most frequent one, or several concurrent spellings. We selected ten auditory word forms, based on 2 criteria: each should correspond to at least 3 words with different spellings, and one of those spellings should have a substantially higher frequency of occurrence than the others, according to the lexique.org database. We generated the corresponding audio files as before. In order to analyze how synesthetic spellings were selected among the possible spellings, we computed the percentage of participants who reported each spelling over the 10 stimuli, and modeled those values with a general linear mixed-effects model (GLMM), with log frequency and grammatical category (noun vs other) as fixed factors, and stimulus identity as random factor.

iv. Pseudowords

Pseudowords are well-formed phonological strings which differ from real words only in that they have not been encountered before and are therefore absent from the mental lexicon (e.g. CHADOURNE in French). They can be spelled-out only on the basis of the statistics of phoneme-to-grapheme correspondences. By presenting pseudowords, we wished to determine whether such non-lexical sound-to-spelling mechanisms also controlled the content of subtitles. Using the UniPseudo tool available on <http://www.lexique.org>, we

created 10 6-phonemes pseudowords, and generated the corresponding audio files as previously described.

4. Results

We identified 26 participants with TTS, and asked them to answer a detailed questionnaire, including mostly retrospective questions on the synesthesia, plus a set of auditory files for which they were asked to transcribe the triggered subtitles. We will report in turn the participants' general characteristics, the individual history of TTS, the subjective visual and temporal features of the subtitles, the specifics of subtitles evoked by number words and other types of auditory stimuli, the varieties of overt and covert speech triggering TTS, and finally the participants' ability to exert voluntary control over TTS synesthesia.

A. Demographic features of participants with TTS

We first determined the demographic features of participants, and their personal and family history of synesthesia.

Demographics. All 26 participants were French native speakers (see Table 3.1; 9 male; median age: 40 years). Birth was normal in 18 participants (69%), 0 were born prematurely, and 8 had other birth complications. Most of them (25/26, 96%) had a higher educational level, while one stopped after middle school. Twenty-four (92%) had normal sight with or without correction. All had normal hearing.

Cognitive development. All participants had normal cognitive development. None reported dyspraxia, autism spectrum disorder, dyslexia or delayed language acquisition.

Reading habits. Regarding reading habits during childhood, 20 participants (77%) considered themselves as avid readers, 4 (15%) as standard readers, and 2 (8%) as occasional readers. During adulthood, 17 participants (65%) still read a lot, 6 (23%) were standard readers, and 3 (11%) were occasional readers.

Associated types of synesthesia. Eighteen participants (69%) reported other associated types of synesthesia (Table 3.2), mostly space-time in 12 (46%), number-space in 9 (35%), and

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sound-color in 7 (27%). Ten participants (38%) had more than one associated synesthesia, and 1 participant (4%) had 7 associated synesthesias.

Table 3.1

N = 26	
Male	9 (35%)
Median age (range)	40 (18-70)
Problems at birth	8 (31%)
Higher education	25 (96%)
Normal cognitive development	22 (85%)
Family history of TTS	9 (35%)
Family history of other types of synesthesia	7 (27%)
Associator synesthetes	18 (69%)
Projector synesthetes	2 (8%)

Table 3.1. General characteristics of participants

TTS: Tickertape synesthesia.

Family history. Nine participants (35%) had other TTS subjects in their family, 2 (8%) did not, and 15 (58%) did not know. Note that 3 participants belonged to one family, and 2 others to another family. Moreover, 7 participants (27%) had members of their family with other types of synesthesia, 2 (8%) did not, and 17 (65%) did not know.

B. History and general features of TTS

We then analyzed at what age TTS emerged, and how participants became aware of this peculiarity.

Age of onset. Reading acquisition is a logical prerequisite to the emergence of TTS. Indeed, nineteen participants (73%) reported that TTS had been present since reading acquisition (n=11) or for as long as they could remember (n=8); 3 participants reported a later onset during adolescence; the remaining 4 did not know.

Awareness of TTS. Most participants (19/26, 73%) discovered that TTS was an unusual phenomenon only during adulthood (>20 y.o.), 2 (8%) during adolescence (16-20 y.o.), and 3 (12%) during childhood (<16 y.o.). This discovery was fortuitous in 8 participants (31%), 6 participants (23%) became aware of this peculiarity through the advertisement for the current study, and 4 participants (15%) through reading a journal article or watching a documentary. Eight participants did not answer. Finally, 19 participants (73%) had mentioned TTS to their family or friends, 2 had been deliberately hiding it, while the remaining 5 (19%) had simply never mentioned it, not knowing that it was an unusual phenomenon.

An advantage or a disadvantage? Only 4 participants considered that TTS had neither a positive nor a negative impact on their daily life activities. For 12 participants (46%) it was both an advantage and a hindrance, only an advantage for 6 participants (23%), and only a hindrance for 4 (15%). The main subjective advantage was the support for spelling words correctly, and the main disadvantage was difficulty focusing their attention toward a single speaker in crowded places.

Attention and control. For 18 participants (70%), TTS was overall an automatic phenomenon on which they had little or no control. Still, when listening to someone, 7 participants (27%) could voluntarily prevent TTS to occur, while only 5 (19%) could do so when they were speaking themselves. When participants did not pay attention to external speech, e.g. in a restaurant, the unattended speech still triggered TTS in 15 participants (58%).

Table 3.2

N = 26	
Space-Time	12 (46%)
Number-Space	9 (35%)
Sound-Color	7 (27%)

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Grapheme-Color	6 (23%)
Digit-Color	6 (23%)
Ordinal-Linguistic	6 (23%)
Perfect Pitch	3 (12%)
Auditive-Gustatory	2 (8%)
None	8 (31%)

Table 3.2. Associated synesthesias

C. Speech modalities triggering TTS

Participants were then asked to specify which features of speech input were required to trigger TTS.

Types of speech input. The main triggers of each participant are reported in Figure 3.1A. In all participants, TTS occurred when watching someone else speaking (26/26, 100%). In most of them (22/26, 85%), TTS persisted even when the speaker was out of sight. In most participants, their own overt speech (23/26, 88%) and covert speech (23/26, 88%) generally triggered TTS. Moreover, TTS was generally triggered by musical lyrics and movies, by covert reading in half the participants, and a few participants reported seeing subtitles while dreaming.

Non-speech sounds. Other types of sounds triggering TTS according to the questionnaire are reported in Figure 3.1B. TTS occurred in 25 participants (97%) when listening to novel words (e.g. a brand name), among whom 5 reported a different TTS from usual (e.g. two reported “blurry words”); one did not know. TTS occurred in 12 (46%) participants when listening to human noises (e.g. laughs or cries), 11 (42%) for non-human noises (e.g. bird song), and in only 5 (19%) when listening to music without lyrics.

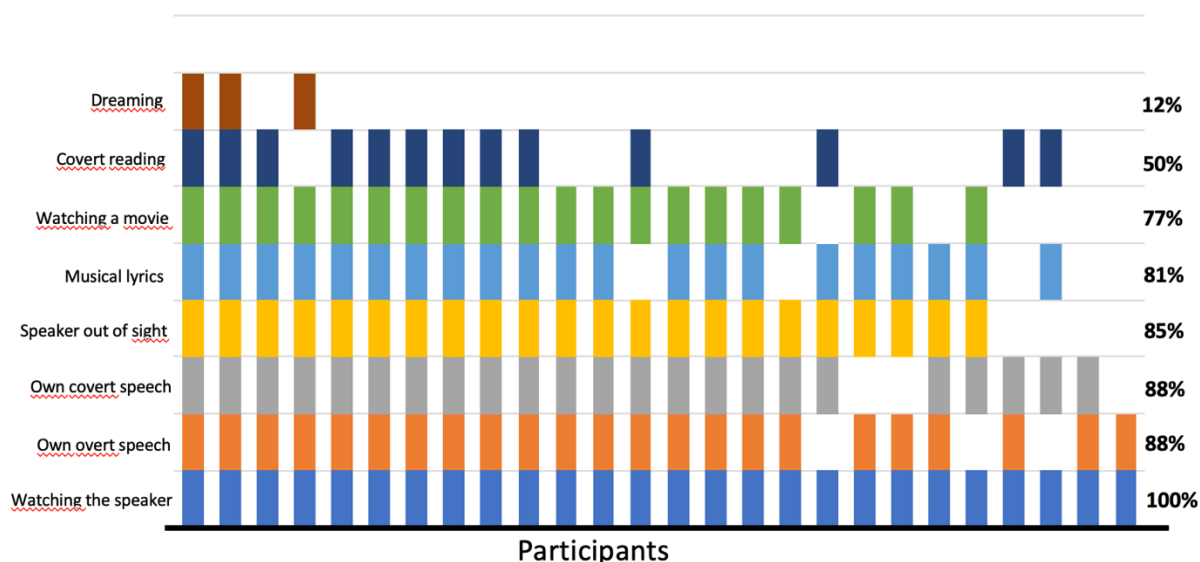
Voice features. Finally, some speech variations influenced the visual properties of subtitles. Subtitles were modified when hearing emotional speech in 9 participants (35%; e.g. “it may change the color of words”, “letters may be blurred or shaking when I’m moved”, “words are

larger for strong emotions”), when hearing louder vs. softer voice in 7 (27%; e.g. “words are bigger for louder voices”), when hearing song lyrics in 5 participants (19%; e.g. “words are less visible than in normal speech”, “words seem to undulate according to the melody”), while pitch had an impact only in 1 participant. The gender of the speaker had no reported impact. In 10 participants (38%), none of these factors affected the synesthesia.

Figure 3. 1

Spoken triggers of ticker-tape synesthesia

A. Types of speech input



B. Non-speech sounds

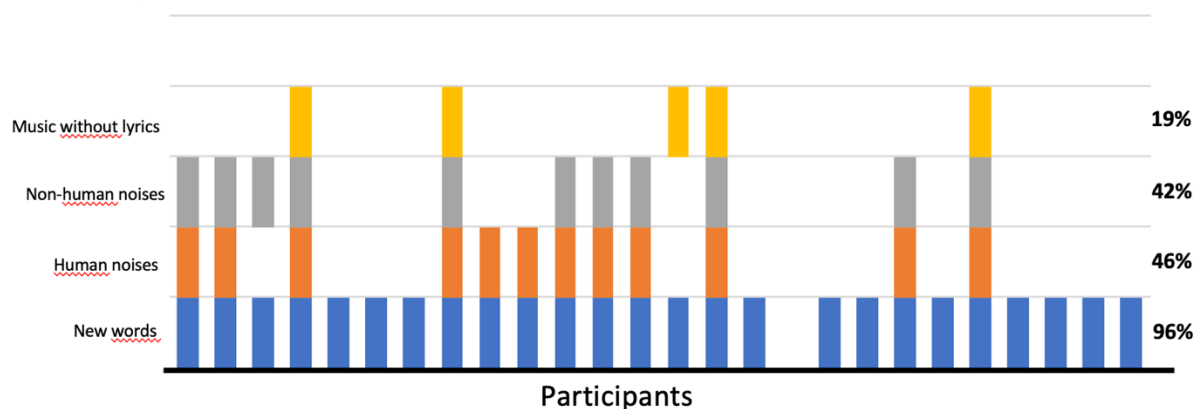


Figure 3. 1

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A. Summary of stimuli triggering tickertape synesthesia (TTS) based on the 26 participants' introspection. Each vertical bar represents a participant. Participants are sorted by decreasing number of trigger types. Each horizontal color line represents one trigger type. Triggers are sorted by decreasing number of concerned participants. Speech emitted by a visible speaker was a constant trigger, other varieties of speech triggered TTS in at least 20/26 participants. Covert reading was reported as a trigger in only 13/26 participants. TTS during dreaming was reported by only 3 participants. **B.** Summary of non-speech sounds triggering TTS based on the participants' introspection. The participants are sorted in the same order as in Figure 3.1A. Each horizontal color line represents one trigger type. Triggers are sorted by decreasing number of concerned participants. Almost all participants reported TTS when listening to novel words, while only 5/26 (19%) when listening to music without lyrics.

Percent values on the right represent the proportion of participants in whom TTS was elicited by the corresponding trigger.

D. Visual features of subtitles

We then collected information on the subjective visual features of subtitles evoked during speech perception.

Projection or association. Grapheme-color synesthetes are commonly distinguished in "projectors" and "associators", as defined by Dixon et al. (2004) depending on their external or internal perception of letter colors. In the case of TTS, 18 participants (69%), visualized subtitles within their internal mental space, while in 2 participants (18%), subtitles were perceived as projected in the outside world. Six participants (23%) reported variability between these two options, and one participant did not answer.

Location. The localization of subtitles was definite and stable in 18 participants (69%). Among those, subtitles were near the speaker's mouth in 4 (15%), or for instance "roughly at the same place as film subtitles, with a right or left shift depending on the origin of the voice", "in the center of my visual field", "behind my eyes". The location was definite but variable in 4 participants (15%). Finally, 4 participants (15%) reported no well-defined location.

Distance. Subtitles were considered as “nearby” in 15 (58%) participants, “far away” in 2 participants, 2 others chose both options, while 4 (15%) provided a precise location specified either in terms of distance (50 cm and 3 m) or more specifically (close to the speaker or within her own head). Three did not know.

Visual attributes. We then explored the font and color of the subjective display. Nineteen participants (73%) variably visualized words in lower- or upper-case, while 7 (27%) only in lower-case. No participant visualized words only in upper-case. Twenty participants (77%) visualized words written only in black, white or grey, while 4 others (15%), who all had associated grapheme-color synesthesia, saw colored letters (some including black/white letters). Two participants did not know. Character size was larger than in regular books in 12 participants (46%), had the same size in 8 (30%), and was smaller in one. Five participants did not know.

Content of subtitles. Seventeen participants (65%) perceived several words at the same time, 6 (23%) were limited to one word at a time. The span was reported as variable by 2 participants (8%). One participant could not answer.

Interaction with reading. When reading in a silent place, 12 participants (46%) visualized only the printed words, 12 (46%) perceived the printed text itself, plus a synesthetic version of the same text. The pattern was variable in 2 participants.

When reading while surrounded by people talking, TTS interfered with reading in 23 participants (88%). In 16 participants (62%), this resulted in an mingling of printed words and subtitles (e.g. “speech is intruding in the written text” or “polluting” it), 4 participants (15%) visualized both texts but in distinct mental spaces (e.g. “I’m seeing the subtitles ‘above’ the printed text”, or “I can arrange the two channels in two parts of my head”), one managed to visualize only the printed words when focusing his attention, and 5 (19%) did not know.

Subtitled movies. When watching movies with subtitles, 11 participants (42%) saw both the real subtitles, and synesthetic subtitles in the original language spoken by the actors, sometimes at different locations. Some participants reported that for this reason watching subtitled movies required massive attentional effort. Nine participants (34%) saw only the real

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subtitles. In 4 participants (15%), the pattern was variable and depended on the familiarity of the spoken language.

E. Temporal features of subtitles

Next, we asked participants to describe how the content of TTS was dynamically updated during continuous speech perception.

Delay between speech and TTS. The onset of the synesthesia was immediate in 19 participants (73%), delayed in 6 (23%). One participant did not know.

Updating of subtitles. The content of TTS was updated by chunks of several words appearing simultaneously in 8 participants (31%), one word at a time in 7 (27%), only letter by letter in 1, and in a variable manner in 10 (38%). New words appeared at the same location as those they were replacing in 14 participants (54%). They scrolled from one side to the other “as if on a conveyor belt” in 9 (35%) participants, while 2 others referred to “bubbles” or “a prompter”. Two participants did not know.

Persistence of subtitles. After their appearance, subtitles persisted briefly in 17 (65%) participants, disappeared immediately in 3 (12%) and had a more variable duration in 5 (19%). Complementing this admittedly vague labelling, a participant mentioned that the last word of an utterance lasted longer as it was not replaced by the following one, and another one that the duration of the subtitle was shorter during fast speech and longer if the speech flow was slower. Those anecdotal reports suggest that subtitles have a perceptible intrinsic duration, which was shortened by the occurrence of subsequent words. One participant did not know.

F. Synesthesia for number words

Number words and ordinary words all feature phonological, orthographic, and semantic representations. However, in addition to those shared formats, numbers may also be represented as Arabic numerals, requiring dedicated mechanisms for recognizing numerals and transcoding them to and from other word representations. We therefore explored to

what extent number words would elicit alphabetic (e.g. “thirty”) or Arabic (e.g. “30”) subtitles, depending on the context in which number words were used.

Numbers denoting quantities. When numbers were used to denote quantities (e.g. “there are 35 people in the room”), 14 participants (54%) visualized them as Arabic digits, 5 participants (19%) as a mix of digits and letters, and 3 participants in alphabetic form only. Four participants (15%) did not know.

Indefinite article. In French, the same word “un/une” is used to express the indefinite article “a” and the unity numeral “one”. When the number was used as an indefinite article (e.g. “j’ai UN ami”), 23 participants (88%) saw it in letters, 1 in digits, one saw both letters and digits, and one did not know.

Mental calculation. When performing mental calculation, 24 participants (92%) mentally saw numbers as Arabic digits, one saw both digits and letters, and one did not know. Moreover, one participant described visualizing geometrical shapes which combined depending on the operation, and another perceived numbers as dots on dice.

Date and hour. When hearing number words in the context of dates, 20 participants (77%) visualized them as digits, 4 saw a combination of digits and letters, and 2 did not know. When numbers were used to express time, 16 participants (62%) saw digits, 3 (12%) saw letters (accompanied by a clock face in one case), 4 (15%) saw a combination of both, 1 only visualized a clock face, and 2 did not know.

Weights and sizes. Finally, for weights and sizes, 21 participants (81%) visualized numbers as digits, 3 (12%) both in digits and letters, and 1 in letters only. One did not know.

G. TTS and the two spelling routes

When hearing novel words for the first time, we ascribe them a phonological representation, and we can spell them according to the statistics of phoneme-grapheme correspondence. Parallel to this “surface” spelling route, upon hearing a known word, a “lexico-semantic” route allows for the retrieval of the stored orthography, which is particularly required for exception words whose spelling does not obey usual phoneme-grapheme correspondence (e.g. PINT or

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HAVE in English), and homophone words, whose correct orthography depends on the semantic and syntactic context (e.g. STAIR-STARE).

Novel words. According to the introspective questionnaire, novel words (e.g. brand names or family names) triggered TTS in 20 participants (77%), while 5 (19%) visualized only few letters, and 1 had no synesthesia. Participants were presented with recordings of 10 pseudowords. All participants experienced TTS, which occurred in 248/260 (95%) trials (e.g. most of participants see SOLQUIN for [sɔlkɛ̃], or see GARMULE for [gɑ̃myl]). In 25 participants, the synesthesia was subjectively as automatic and fast as for real words.

Exception words. The 26 participants were presented with recordings of 9 exception words (a tenth one was excluded due to poor recording quality), and they all experienced TTS. We excluded from further analyses 2 participants who did not report the orthographic content of the subtitles. On 167/216 (77%) trials, participants perceived words in their correct spelling. On 32/216 (15%) trials, they perceived an phonologically plausible but lexically incorrect spelling (e.g. YOTE instead of YACHT; RESPE instead of RESPECT). Occasionally, (9/216 trials, 4%) both the correct and an incorrect spelling were perceived (e.g. LONGTEMPS and LONTANT; FEMME and FAME; YOTE then turning into YACHT). There was thus a strong preponderance of lexical spelling, followed by a substantial minority of trials with phonological spelling. A few participants showed an atypical pattern.

Homophones. Finally, participants were presented with 10 homophone words. One participant did not answer. On most trials (189/250, 76%) participants perceived only a single spelling of the target. Some participants sometimes saw more than one spelling, either in succession or simultaneously. In order to formally assess the observation that most responses consisted in relatively frequent nouns, we restricted the analysis to the 189 trials with only one single reported spelling, considering only the 3 most frequently reported spellings for each stimulus. Using a GLME (see Methods) we found that the likelihood for a spelling to be reported was higher if it corresponded to a noun than to another grammatical category ($p = 0.005$), and to a higher- than to a lower-frequency word ($p = 0.01$).

Foreign language. Speech perceived in an unfamiliar language may be processed and spelled out in the same way as novel words, provided that a well-defined phonological representation can be computed. According to the introspective questionnaire, when hearing a known

foreign language, 17 participants (65%) reported having TTS, 7 (27%) had TTS but to a lesser extent than in their native language, and 2 (8%) had no synesthesia at all. When hearing an unknown language, TTS was reduced to a few sparse letters in 16 participants (62%), occurred roughly like in the usual language in 5 (19%) and did not occur at all in 5 other participants.

H. Synesthesia for non-speech sounds

Even vocal (e.g. laughing) or non-vocal noises (e.g. explosion) may be spelled out as onomatopoeias. We therefore studied whether such auditory stimuli would also trigger TTS.

According to the introspective questionnaire, at least some non-speech sounds triggered TTS in 14/26 participants (54%), including non-human noises (e.g. bird songs or the sound of a bell), and human noises (e.g. laugh or sneeze). In 11 participants (42%), none of these stimuli triggered TTS. One participant did not know. Participants were presented with 13 recordings of animals, human non-speech sounds, and noises of objects. Animal sounds triggered TTS on 69/104 (66%) trials. All but two participants had a visual perception for at least one sound, ranging from 9/26 for the rooster (seen e.g. as “HUHUHU”), to 24/26 for a cat meowing (generally perceived as the onomatopoeia “MIAOU”). Human noises triggered TTS on 57/104 (55%) trials. All participants experienced TTS for at least one human noise, ranging from 9/26 for a cough (seen e.g. as “HEU-HEU” or “KHU”) to 26/26 for laughs (generally perceived as variants of “AHAHAH”). Noises of objects triggered TTS on only 42/130 (32%) trials. Only 18 participants reported TTS, ranging from 5/26 for a bell sound or a gunshot (one participant saw “TIR”, the French word for shot) to 13/26 for an alarm clock or an ascending musical scale (most of them seeing the words DO RE MI etc).

5. Discussion

This study is a first attempt at systematically gathering descriptive data on TTS, and at providing an overview of its spectrum. This is necessary ground work, preliminary to subsequent studies of TTS, rather than the test of detailed predictions. Our only background hypothesis is that TTS reflects an enhanced top-down influence of speech processing on orthographic representations, in the form of vivid and automatic mental images of written words. We will now summarize our main findings, relate them to general concepts in the fields

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of synesthesia and written language processing, and put forward some specific questions and propositions for future studies.

A. Is TTS an exceptional phenomenon?

Over a few months, we identified 26 synesthetes with reasonable ease. Although we cannot provide a reliable estimate of TTS prevalence in the general population, this suggests that TTS may be in the range of a few percent, similar to other better documented synesthesias. The prevalence of 7% suggested by Chun and Hupé (2013) would place TTS above perfect pitch (0.06%, Profita et al., 1988) and grapheme-color synesthesia (1.2%, Carmichael et al., 2015), and below sequence-space (11%, Sagiv et al., 2006) synesthesias. However, the 7% figure is probably a gross overestimation, due to sampling biases. Still, the intuition that TTS would be a highly exceptional phenomenon is clearly misleading, as first suggested by Holm et al. (2015). As most synesthesias, TTS is purely subjective, it is not associated with outstanding abilities or incapacitating impairments, and its existence is generally ignored. Hence it fails to be identified by either synesthetes or their acquaintances. Indeed, in our study, more than 2/3 of participants became aware of the peculiarity of TTS during adulthood, or even only upon reading our recruitment poster.

We found a non-significant 2:1 female/male ratio among participants, which falls in the broad span of previous estimates, ranging from 6:1 (Baron-Cohen et al., 1996; Rich et al., 2005) to 1:1 (Simner et al., 2006). Meta-analyses suggest that sex differences are actually fragile (Simner and Carmichael, 2015) and might be attributed to a self-referral bias, with a higher propensity of females to self-report atypical experiences in general (Dindia and Allen, 1992).

Among our participants, more than 2/3 reported associated synesthesias, space-time synesthesia being the most frequent (52%). Such multiplicity is commonly reported in the synesthesia literature, and is suggestive of common underlying developmental mechanisms (Ward, 2013). Similar to Holm et al. (2015), we found no outstanding link between TTS and grapheme-color synesthesia, which was still present in 6 (23%) of participants. Note that we considered perfect pitch as a type of synesthesia, although this condition is more often considered in the context of music perception (for reviews see Carden and Cline, 2019; Hou et al., 2017). Although this stance may be disputable (for a detailed comparative discussion

see Glasser, 2021), perfect pitch fits the definition of synesthesia as stimulation in one sensory or cognitive domain (pitch perception) automatically inducing an unusual and vivid perception in a distinct sensory or cognitive domain (note label). Beyond anecdotal associations in individual persons (e.g. Bernard, 1986; Bouvet et al., 2014; Lebeau et al., 2020), this view is supported by a high frequency of other synesthesias (about 20%) (Gregersen et al., 2013) in individuals with perfect pitch, possibly reflecting phenotypic and genetic relationship (Gregersen et al., 2013; Hänggi et al., 2008). Although the number of participants in the present study is limited, and the prevalence of perfect pitch is highly variable across studies and populations (Glasser, 2021), a proportion of 12% of perfect pitch among our 26 TTS participants, may be viewed with caution as suggestive of an increased incidence.

We also found that about 1/3 of our participants had cases of TTS in their close family. Again, such family predisposition was observed by Galton (1883) and is in line with more recent evidence. Thus Ward and Simner (2005) reported a 16% prevalence inside the families of synesthetes, as compared to 4.4% in the general population (Simner et al., 2006), pointing to the importance of genetic factors (Asher and Carmichael, 2013).

Future controlled studies of prevalence, gender ratio, family history, association with other synesthesias or developmental disorders, and genetics, should allow for a better understanding of the origins of TTS.

B. The paths from sounds to letters in TTS

TTS is by definition triggered by the perception of speech. What are however the features of speech which are necessary and sufficient, and what are those that modulate the content of TTS subtitles?

Internal phonology. All participants experienced TTS when hearing and watching someone else speaking. In the vast majority of cases, TTS persisted when the speaker remained out of sight, or when participants were speaking themselves. However, what was critical was not the presence of overt speech, but the activation of an internal phonological code. Thus, TTS was usually triggered also by inner speech, a covert phonological stream with no acoustic counterpart (Levelt, 1989). Moreover phonologically irrelevant factors, such as the gender of the speaker, had generally no impact on TTS. The efficiency of only “thinking about” the inducer may actually be a common feature of many synesthesias. Thus most

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grapheme-color synesthetes assert that letters or numbers that they imagine have the same color as when they see them on the page (Edquist et al., 2006; see also Gould et al., 2014). The abstract nature of the inducer was nicely illustrated by Mroczko (1997): in grapheme-color synesthesia, the color of letters is immediately transmitted to novel letter shapes upon learning their graphemic value. We therefore predict that brain imaging should reveal a common activation pattern during TTS, irrespective of the overt or covert type of speech input.

Interestingly still, a few participants reported that their own speech or the speech of hidden speakers did not generate TTS (Figure 3.1). In both circumstances, attention may not be focused on the speech stream: speakers who are out of sight are often irrelevant and should be filtered out; and speakers attend to the communicative intent rather than to the sound content of their own utterance. This may result in weaker TTS, or in under-reporting of TTS under those conditions. An alternative account would refer to the tight links that have been proposed between lip-reading and word reading, and the involvement of the left VOT cortex in both abilities (Campbell et al., 1986; Thomas Hannagan et al., 2015). One may speculate that in some synesthetes, generating TTS would require combined top-down input to the VWFA, not only from phonology but also from face perception systems.

Non-lexical phonology. Real words have a phonological representation stored in the mental lexicon, but we also manipulate speech sounds in non-lexical contexts, for instance when hearing or reading aloud novel words. In all participants, TTS was triggered by real words, but also by pseudowords, showing again that phonology is critical, irrespective of its lexical or non-lexical source. Even non-speech sounds sometimes elicited TTS, in-as-much as they underwent phonological coding. Thus, one participant told us that a bird used to sing in his garden early in the morning. After a few days he translated the song into an onomatopoeia. From this moment on, the bird's song triggered the synesthetic perception of the written form of the onomatopoeia. A similar logic applies to the triggering of TTS by foreign speech. We therefore predict that the typical brain activation pattern of TTS should appear in the minimal contrast between non-speech noises before vs after learning associated onomatopoeias (Taitz et al., 2018), or between degraded speech before vs after perceptual training (Davis et al., 2005).

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From phonology to orthography. The translation from phonology to orthography in TTS followed the parallel pathways featured by the classical two-route model of spelling and reading (Coltheart, 2006; Perry et al., 2007; J.S. Taylor et al., 2013). Thus, synesthetic pseudowords were usually spelled according to the most frequent phoneme-grapheme correspondences (phonological route), while exception words were spelled according to their stored orthography. Homophone non-homograph words (e.g. LEAK vs LEEK) were perceived more often under their most frequent orthography, a further trace of lexical processing.

Moreover, when TTS was triggered by non-speech noises, TTS occasionally disclosed a contribution of semantic knowledge. First, the content of the TTS sometimes corresponded to a largely conventional phonological code. Thus the “DRIIING” spelling often elicited by the sound of an alarm clock may not be its most faithful translation, but it is its usual literary depiction, e.g. in comic strips. Meowing elicited the very familiar “MIAOU” in almost all participants, while the less familiar call of a rooster was a less effective inducer. The same trend prevailed for other categories of noise: laughter was more effective than cough, and alarm-clock ringing than gunshot. Other types of synesthesias also are more vivid for more frequent inducer-concurrent associations (Beeli et al., 2007). Second, some participants, instead of seeing an onomatopoeia, visualized the written name of the object generating the noise. For example, some participants saw the French word for “GUN” or “GUNSHOT” when hearing the noise of a gunshot. It is likely that the synesthete identified the noise, internally produced the corresponding word, which then entered in the common TTS pathway.

The case of number words. In addition to generic orthographic coding (THIRTY), numbers can be written using Arabic numerals (30). Across participants, there was a remarkable variety in the relative contribution of the two codes to TTS, and mixtures of both were not uncommon (e.g. one participant reported when asked about the date that he saw “the numbers of the day in Arabic numerals, months in letters, and year in numerals”; another reported about the number 35 that he saw “letters and numerals overlapping”). This may be similar to the collisions occurring with exception words, which sometimes induced the near simultaneous perception of the lexical and phonological spellings (e.g. FEMME and FAME). Such collisions indicate that TTS subtitles can be fed with the output of whatever route linking phonology to orthography.

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Discussion

In summary, TTS resulted from the translation from phonology to orthography through phonological and lexico-semantic routes. Importantly, even neurotypical individuals show behavioral evidence of phonological influence on visual word recognition. First, there is implicit and automatic activation of orthographic codes during speech perception. For example, during purely auditory lexical decision, latencies are shorter for words with a consistent than with an inconsistent spelling (Ziegler et al., 2008), an effect which disappears under TMS of the SMG (Pattamadilok et al., 2010). Similarly, also during auditory lexical decision, prime words facilitate targets in proportion to their orthographic overlap (Chéreau et al., 2007). Second, phonology does actually modulate the recognition of printed words. For instance, during lexical decision and naming with visual words, responses are facilitated by primes with a purely phonological link to targets (Carreiras et al., 2005; Grainger et al., 2006). In this context, TTS may be viewed as an exceptionally vivid access to orthographic representations which are activated even in non-synesthetes, implying some continuity between normal speech perception and TTS, a controversial issue in the field of synesthesia studies (Deroy and Spence, 2016; Martino and Marks, 2001).

In a recent single-case fMRI study of TTS, we used dynamic causal modeling and showed that indeed TTS induced by spoken words and pseudowords relied on the top-down flow of information along distinct routes, involving the supramarginal and middle temporal gyri, respectively (Hauw et al., 2023c). Future studies should resort to time resolved methods such as EEG/MEG in order to decipher the temporal course of the alternative processes leading to TTS.

C. Visual features of TTS

All participants were able to report with some precision the core visual features of TTS in terms of location, distance, color, or case. While orthographic imagery exists to some degree in all literate individuals (Bourlon et al., 2009; Holm et al., 2015), tickertapers feature a particularly vivid form of such imagery, possibly correlated with higher activations in the VWFA (Fulford et al., 2018; Hauw et al., 2023c).

The precise features of synesthesias (e.g. what is the color of a specific letter?) are at least partially determined by personal experience (Rich et al., 2005; Ward and Simner, 2003; Witthoft and Winawer, 2006). In the case of TTS, the black color of subtitles may reflect the

usual color of printed words, and their location at the bottom of the visual field or next to the speaker's mouth may result from the position of actual subtitles and of comic bubbles.

Four participants perceived colored TTS subtitles. They all had associated TTS and grapheme-color synesthesia. To their mind's eye, letters in the subtitles were colored in the same way as external letters, revealing the chaining of the two synesthesias, mapping phonology to orthography, and then orthography to colors. In 9 other participants, the visual features of subtitles were modulated by the emotional content of the input. In various synesthesias also, emotions elicited by the inducer may modulate the features of the concurrent (for a review, see Dael et al., 2013). It may even occur that "emotional states as such exist as colors projected out in the visual field, (...) and the intensity and prevalence the color are a measure of the intensity of the emotional reaction" (Cutsforth, 1925). This may suggest that in our 4 participants, TTS was associated with a putative "affective synesthesia".

In grapheme-color synesthesia, distinction is commonly made between a majority of "associators" and a minority of "projectors", who feel that illusory colors exist in their mind or in the outside world, respectively (Amsel et al., 2017; Dixon et al., 2004). Although the distinction may not be always clear-cut, we found a similar predominance of TTS associators (69%). This distinction putatively results from differences in the anatomical connectivity among involved brain areas (Rouw and Scholte, 2007), or in the pattern of their functional cross-talk (Amsel et al., 2017; van Leeuwen et al., 2011). Assuming that TTS associators and projectors put into play regions involved in mental imagery and perception, respectively (Pearson, 2019; Spagna et al., 2021), one may predict that the two groups should differ in the relative involvement of high-level infero-temporal areas such as the VWFA, vs. of low-level visual cortex.

In future research it may also be interesting to investigate the visuo-spatial arraying of the alphabet in the mental imagery of TTS individuals (Jonas et al., 2011), as it may potentially differ from participants with typical relationships between phonology and orthography.

D. Dynamic features of TTS

Qualitative introspective reports are obviously inadequate to characterize the fast time course of TTS. One may only observe that the life span of images is at most in the order of seconds, that they are rapidly flushed by the following ones, and that they encompass from

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one to a few words. Those features are suggestive of a short term memory system, possibly identical to the so-called graphemic buffer, a device which has been studied mostly in the context of word spelling. It is thought to maintain an orthographic representation of the current word during writing or typing (Buchwald and Rapp, 2004), but it is also involved to some extent in reading (Caramazza et al., 1996; Purcell et al., 2017). In this context, TTS might be considered as the result of a hyperactive graphemic buffer, supporting enhanced visual images. This could indeed explain why 10 (38%) participants considered that being endowed with TTS facilitated writing. Future studies should study the links between TTS and writing performance, and resort to time-resolved methods to assess the time course of the processes underlying TTS.

E. The pros and cons of TTS

Easier writing and better orthography is the only advantage consistently acknowledged by tickertapers. In grapheme-color synesthesia, which like TTS is closely dependent on literacy, synesthetes seem to benefit from a modest but replicable advantage in verbal and other memory tasks (for a review see Rothen et al., 2012). More recently, Smees et al. (2019) showed that 10-11 year-old synesthetes have better expressive and receptive vocabulary than control children. This advantage did not exist before elementary school, suggesting that synesthesia yielded a verbal learning advantage. In the case of TTS, one may predict that effortlessly enjoying a stable and vivid orthographic representation should help tickertapers to learn to read and write.

Conversely, most participants reported that TTS makes it difficult for them to focus their attention, for example when trying to read in public spaces, or to follow one among several ongoing conversations. Attentional effort allowed some of them to get rid of the irrelevant channel, for instance by putting actual printed words and concurrent TTS subtitles in different “mental spaces”.

In summary, factual evidence is missing on the practical pros and cons of TTS. We predict that tickertapers should be better than controls in tasks based on stable orthographic imagery, such as writing long and complex words, or letter counting, backward spelling, or

visual rhyme judgment with spoken words. Conversely, concurrent speech should interfere with e.g. visual lexical decision more detrimentally in tickertapers than in controls.

6. Conclusion

Generally considered an anecdotal and exceptional phenomenon, tickertape synesthesia provides a novel gate in the mechanisms of reading and reading acquisition. Similar to dyslexia, it results from an atypical setup of the cerebral reading machinery. We reported a descriptive study of tickertape synesthesia in a group of 26 participants, based on detailed introspective questionnaires and on the presentation of controlled auditory stimuli. This groundwork leaves a number of questions open for future research. Empirical studies should address (1) the genetic and environmental bases of TTS; (2) the objective behavioral markers of TTS. This is particularly important, not only for the understanding of the cognitive underpinnings of TTS, but also for developing objective criteria for ensuring the genuineness of TTS beyond subjective self-report; (3) the development of orthographic imagery and the emergence of TTS in children with or without dyslexia; (4) the cerebral mechanisms of TTS using multimodal brain imaging in adults and children; (5) the brain correlates of individual variability in TTS phenotype.

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Conclusion

We were therefore able to better describe certain visuo-spatial aspects of synesthesia, and provide details of what happens in certain circumstances, as well as the presence of subtitles when listening to certain noises or pseudo-words. The next step was to identify objective markers of this phenomenon, with behavioral tests in which synesthesia could be an advantage or disadvantage.

CHAPTER IV

Advantages and disadvantages of TTS



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Research Report

The advantage of being a synesthete: The behavioral benefits of ticker-tape synesthesia



Fabien Hauw ^{a,b,*}, Mohamed El Soudany ^a and Laurent Cohen ^{a,b}

^a Inserm U 1127, CNRS UMR 7225, Sorbonne Universités, Institut du Cerveau, ICM, Paris, France

^b AP-HP, Hôpital de La Pitié Salpêtrière, Fédération de Neurologie, Paris, France

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ABSTRACT

As first described by Francis Galton, some persons perceive vividly and automatically in their mind's eye the written form of words that they are hearing. This phenomenon, labeled ticker-tape synesthesia (TTS), is thought to reflect an abnormally strong influence of speech processing in language areas on to orthographic representations in the visual cortex. Considering the relevance of TTS for the study of reading acquisition, we looked for objective behavioral advantages or impairments in 22 synesthetes, as compared to 22 matched control participants. In three auditory tasks relying on orthographic working memory (letters counting, backward spelling, and letter shape decision), we predicted and observed better performance in synesthetes than in controls. In two visual tasks (lexical decision and letter decision) with a concurrent auditory stimulation, we predicted that synesthetes should suffer from a larger interference by irrelevant speech than controls, but eventually found no difference between the groups. Those results, which we discuss in relation to orthographic processing, mental imagery, and working memory, promote TTS from pure subjectivity to an experimentally measurable phenomenon.

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The advantage of being a synesthete: the behavioral benefits of tickertape synesthesia

Fabien Hauw^{a, b}, Mohamed El Soudany^a, Laurent Cohen^{a, b}

a. Inserm U 1127, CNRS UMR 7225, Sorbonne Universités, Institut du Cerveau, ICM, Paris,
France

b. AP-HP, Hôpital de La Pitié Salpêtrière, Fédération de Neurologie, Paris, France

1. Abstract

As first described by Francis Galton, some persons perceive vividly and automatically in their mind's eye the written form of words that they are hearing. This phenomenon, labeled tickertape synesthesia (TTS), is thought to reflect an abnormally strong influence of speech processing in language areas on to orthographic representations in the visual cortex. Considering the relevance of TTS for the study of reading acquisition, we looked for objective behavioral advantages or impairments in 22 synesthetes, as compared to 22 matched control participants. In three auditory tasks relying on orthographic working memory (letters counting, backward spelling, and letter shape decision), we predicted and observed better performance in synesthetes than in controls. In two visual tasks (lexical decision and letter decision) with a concurrent auditory stimulation, we predicted that synesthetes should suffer from a larger interference by irrelevant speech than controls, but eventually found no difference between the groups. Those results, which we discuss in relation to orthographic processing, mental imagery, and working memory, promote TTS from pure subjectivity to an experimentally measurable phenomenon.

2. Introduction

In 1883, Francis Galton first reported that “some few persons see mentally in print every word that is uttered (...) and they read them off usually as from a long imaginary strip of paper”, a phenomenon termed tickertape synesthesia (TTS; Galton, 1883). Reading acquisition rests on the development of novel links between the recognition of written signs by the visual system, and language processes including access to speech sounds and meaning (Dehaene et al., 2015). Thus TTS may be viewed as the symptom of an atypical development of such links, whereby speech perception causes an unusually vivid and irrepressible perception of orthography in the mind’s eye. As such, on a par with dyslexia, the study of TTS may provide a window to the mechanisms of normal and impaired reading acquisition.

In a recent group study, we showed that TTS may not be as uncommon and anecdotal as previously thought, and we provided a systematic analysis of the rich subjective reports collected in TTS participants (Hauw et al., 2023a). Essentially subjective phenomena, however, are not easily amenable to experimental study, as shown by the complex history of the cognitive neuroscience of consciousness (Hohwy and Frith, 2004). In the field of synesthesia research, this has led to attempts at finding measurable behavioral differences between synesthetes and controls beyond introspective report. Particularly, studies of grapheme-color synesthesia, in which letters and digits are each endowed with a perceived color, have looked for evidence that the illusory colors may help or hinder synesthetes in various psychophysical tasks, e.g. detecting 2s amongst 5s with the support of their distinct synesthetic colors (Hubbard and Ramachandran, 2005; Rich and Karstoft, 2013; Ward et al., 2010).

Considering the relevance of TTS for the study of reading acquisition, and for the general field of synesthesias, we looked for measurable behavioral advantages or impairments in synesthetes relative to typical participants. In our previous study, the main subjective advantage reported by synesthetes was support for spelling out words, and the main disadvantage was difficulty focusing their attention toward a single speaker in crowded places (Hauw et al., 2023a). A panel of behavioral markers would provide objective measures for identifying synesthetes, understanding the cognitive underpinnings of TTS, studying individual variability, and perform correlational brain-behavior imaging studies of synesthesia (Hauw et al., 2023c).

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Based on introspection, TTS provides an immediate and vivid representation of the orthography of spoken words, sustained for an appreciable duration provided that the image is not immediately superseded by upcoming words. We reasoned that such enhanced orthographic working memory should provide support in orthographic tasks on spoken input. Hence we designed letters counting, backward spelling, and letter shape decision tasks with speech input. Those 3 tasks are relatively difficult to perform mentally (Cohen et al., 2004; Hampson and Morris, 1978; Paulesu, 2001), while they would be trivially easy with an external written support. We therefore predicted that synesthetes should show an advantage over controls, thanks to the stable and vivid perception of the stimuli in their orthographic form, playing the role of an internal written support.

Conversely, we predicted that performing difficult orthographic tasks on written input should be perturbed by the irrepressible intrusion of synesthetic letters induced by simultaneous spoken distractors. We therefore designed tasks of visual lexical decision and letter decision, in which we predicted that synesthetes should suffer from a larger interference by speech than controls.

3. Materials and Methods

A. Participants

We created a short description of what TTS is, and recruited participants by broadcasting it through email and social networks, targeting particularly groups of students and university members, and groups devoted to synesthesia, psychology, and neuroscience. We thus recruited 22 tickertape synesthetes, plus 22 controls matched one-to-one to synesthetes based on age, gender, education level and handedness (Table 4.1). The sample size was thus determined based on the availability of participants from this special population, and having a tickertape synesthesia and being over 18 years old were our only inclusion criteria. We managed to reach a size consistent with current practice in behavioral studies of language processing. All participants were native French speakers, and had no history of neurological or psychiatric disorders. Except for one person, they formed a subset of the participants studied in Hauw et al. (Hauw et al., 2023a). The research was approved by the institutional review board of the INSERM (protocol C13-41), and all participants provided informed written consent in accordance with the Declaration of Helsinki.

Table 4.1

	Synesthetes (N=22)	Controls (N=22)
Males	7 (32%)	7 (32%)
Mean age (range)	36.3 (18.6-70.8)	36.3 (19.5-70.4)
Post-secondary education	21 (95%)	21 (95%)
Right-handed	17 (77%)	17 (77%)

Table 4.1. Demographic features of the participants

B. Experimental tasks

All experiments were implemented using the Psychophysics Toolbox 3 (<http://psychtoolbox.org>) v3 in MATLAB (Mathworks, Natick, MA, USA). The sound files used in Experiments 1, 2, 4 were generated using the ttsreader.com speech generation software, those used in Experiment 3 through the text to speech functionality from Macintosh computer, all with a female voice; sounds for Experiment 5 were recorded, with a male speaker. At the end of each experiment, participants were asked whether they felt that TTS had provided support, hindrance, both, or none to task performance.

Experiment 1: Letters counting

Stimuli consisted of 20 spoken nouns, 5 to 9 letters long (4 words each). All words were 5-phonemes long, in order to avoid any confound between orthographic and phonological length. Their mean log lexical frequency was 1.54 (SD=0.29) (New et al., 2004). Frequency did not differ across words of different length (Kruskal-Wallis $\chi^2(4) = 2.34$, $p = 0.67$). Words were presented one at a time and participants had to indicate their number of letters by typing on the numerical keypad while the rest of the keyboard was masked. Participants were asked to respond as accurately and rapidly as possible. The next stimulus started 1 s after the response.

Experiment 2: Backward spelling

Stimuli consisted of 15 spoken nouns. In order to allow for an independent assessment of syllabic and orthographic length, stimuli included three sets of 5 items: words with 2 syllables and 5 letters, 2 syllables and 8 letters, and 3 syllables and 8 letters. Their mean log lexical frequency was 1.45 (SD= 0.38). Word frequency did not differ between word sets (Kruskal-Wallis $\chi^2(2) = 2.16$, $p = 0.34$). Words were presented one at a time and participants had to spell them backward orally (e.g. DECOR > 'R, O, C, E, D'), as accurately and rapidly as possible. The next stimulus started 2 seconds after the end of the response. Vocal responses were recorded for subsequent scoring of errors and latencies.

Experiment 3: Letter shape decision

Participants were presented with spoken words and had to decide whether, when written in lower-case, those words contained an “ascender” (i.e. a letter with a stroke going above the baseline, e.g. “b”), or a “descender” (i.e. a letter with a stroke going below the baseline, e.g. “p”). Participants were instructed to consider the letter “f” as an ascender.

Stimuli consisted of 90 6-letters words, half containing exactly one ascender, and half exactly one descender. In order to assess the role of within-word position, the target letter was equally often in the first, third or fifth letter position. We used a total of 15 words per type of target (ascender/descender) x position, resulting in 90 different words. Their mean log lexical frequency was 1.11 (SD= 0.66). Word frequency did not differ across positions (Kruskal-Wallis $\chi^2(2) = 0.74$, $p = 0.69$) nor type of target (Kruskal-Wallis $\chi^2(1) = 0.43$, $p = 0.51$). Participants had to press a button with their right or left hand depending on the presence of a descender or an ascender, respectively. The rest of the keyboard was masked. The next stimulus started 1 second after the response.

Experiment 4: Interference of speech on visual lexical decision

Participants performed a visual lexical decision task, while interfering auditory stimuli were presented, consisting of normal or scrambled speech, plus a silent control condition. Visual words and pseudowords were a subset of those used in a previous article (F. Bouhali et al., 2019). We selected 90 French nouns and their matched pseudowords, ranging from 4 to 10 letters. Two words and the corresponding pseudowords were excluded from the analyses for

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technical reasons. The mean log frequency of words was 1.06 (SD=0.71). Normal speech consisted of fragments of the tale Little Thumbling, read by a female voice (available at www.litteratureaudio.com). Scrambled speech stimuli were derived from normal speech using an algorithm preserving the spectral content over long time scales while removing structures at shorter timescales (www.mathworks.com/matlabcentral/fileexchange/29396-time-domain-scrambling-of-audio-signals, Dan Ellis, 2023). Visual stimuli were presented for 50 ms, and immediately followed by a 50 ms mask “#####” (see Supplementary figure 4.1). The stimulus onset asynchrony (SOA) between visual stimuli was jittered, with equally probable durations of 1400, 1550, or 1700 ms. The participants were asked to ignore auditory distractors, and to respond by pressing a button with their right or left hand for real words and pseudowords, respectively. The experiment was divided into 18 blocks, 6 for each auditory condition, in pseudo random order. Blocks had a duration of about 14 s, comprised ten visual stimuli, and were separated from the next one by a 3-seconds pause. Visual stimuli were presented only once. The experiment lasted around 5.5 min.

Experiment 5: Interference of speech on letter decision

Participants performed a visual letter decision task under auditory interference. The experiment consisted of 4 blocks of 30 trials, with a 15 seconds-pause between each block. Each block was based upon 2 out of the letters B, D, P, and R, which were selected due to their visual similarity: D and P, D and R, B and P, and B and R. At the onset of each block, participants were informed of the 2 current letters. On each trial, one of the two current letters was presented for around 8 ms, followed by a 35ms, 45ms or 55ms blank screen, and then by a 100 ms mask made of multiple “#” (see Supplementary figure 4.1). On congruent trials, the target letter was presented during a repeated spoken syllable containing the consonant represented by the target letter (e.g. “bababa” with B). On incongruent trials, the syllable contained the other consonant in the block (e.g. “rarara” with B). The mean duration of the repeated syllables was 1.10s (range 0.97s-1.19s), and visual target letters were presented 100ms before their end. Forty congruent, incongruent and silent trials were presented in pseudo-random order. On each trial participants had to indicate which of the two possible letter they had seen, by pressing on buttons with their left or right hand. The experiment lasted about 8.5 min.

C. Statistical analysis

We analyzed error rates and correct reaction times with generalized mixed-models (GMM) using the Jamovi software (v. 2.3.16.0). We calculated effect sizes using Odds ratio (OR) for error rates, and partial eta squared (η_p^2) for reaction times. In all experiments, participant and stimuli were entered as random effects, and group as a fixed effect. All other within-subject factors were entered as fixed effects. The significance threshold was set to $p < 0.05$. One control participant, who had not correctly understood the instructions, was excluded from the analysis of Experiment 4.

4. Results

A. Letters counting

Participants were presented with spoken words varying in orthographic length, and indicated their number of letters as fast as possible. We predicted that synesthetes should be faster and more accurate than controls (Figure 4.1A).

Synesthetes made fewer errors (15.5% vs 25.7%; $\chi^2(1)=4.94$, $p=0.026$; OR = 2.19, 95% CI 1.10 – 4.36, indicating a small to medium effect) and responded faster (3590 ms vs 4799 ms; $F(1,41)=15.19$, $p < 0.001$, $\eta_p^2 = 0.27$, indicating a large effect) than controls. Moreover, responses to shorter words were more accurate ($\chi^2(4)=30.11$, $p < 0.001$; OR (9-5 letters) = 6.28, 95% CI 3.01 – 13.11, indicating a large effect) and faster ($F(4,15)=30.57$, $p < 0.001$, $\eta_p^2 = 0.89$, indicating a large effect) than to longer words, with no length x group interaction (error rate: interaction $\chi^2(4)=2.74$, $p=0.6$; RTs: interaction $F(4,635)=1.60$, $p=0.17$). We then ran reliability analyses using the splithalf R-package (Parsons, 2021). Using 5000 random splits, as in all subsequent analyses, the Spearman-Brown corrected reliability estimate was 0.75, 95% CI [0.63 - 0.85] for accuracy, and 0.9, 95% CI [0.85 - 0.94] for RTs.

On debriefing, 18 (82%) synesthetes reported that TTS helped them perform the task, while only 4 (18%) reported neither an advantage nor a hindrance.

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B. Backward spelling

Participants were presented with spoken words varying in orthographic and syllabic length, and spelled them backwards orally. We predicted that TTS participants should be faster and more accurate than controls (Figure 4.1B).

Overall, there was only a tendency for synesthetes to make fewer errors than controls (14.8% vs 20%; $\chi^2(1)=1.63$, $p=0.20$), but they responded almost 3 s faster (6985 ms vs 9506 ms; $F(1,41)=11.83$, $p=0.001$, $\eta_p^2 = 0.18$, indicating a large effect). Restricting the analysis to bisyllabic items in order to study purely orthographic length, synesthetes were faster than controls (6083 ms vs 8321 ms; $F(1,41)=12.69$, $p<0.001$, $\eta_p^2 = 0.24$, indicating a large effect). Error rates were higher (24.5% vs 4.6%, $\chi^2(1)=13.96$, $p<0.001$; OR = 10, 95% CI 2.99 – 33.44, indicating a large effect) and responses slower (9444 ms vs 5388 ms; $F(1,8)=18$ $p=0.003$, $\eta_p^2 = 0.7$, indicating a large effect) for 8-letters than 5-letters words. Importantly, this length effect was smaller in synesthetes than in controls (interaction $F(1,325)=8.22$ $p=0.004$, $\eta_p^2 = 0.02$, indicating a small effect). Finally, restricting the analysis to 8-letters items to study purely syllabic length, synesthetes were again faster than controls (8464 ms vs 11624 ms; $F(1,36)=11.4294$, $p=0.002$, $\eta_p^2 = 0.24$, indicating a large effect). There was no effect of syllabic length, and no interaction of length with group. The Spearman-Brown corrected reliability estimate was 0.73, 95% CI [0.6 - 0.84] for accuracy. For RTs, one subject was excluded from reliability analyses because he had only 3 correct answers. The Spearman-Brown corrected reliability estimate was 0.84, 95% CI [0.74 - 0.91].

After the experiment, 20 (91%) synesthetes reported that TTS helped them spelling words backward, while 1 reported a hindrance, and 1 no effect.

C. Letter shape decision

Participants were presented with spoken words, and indicated whether they included a letter with an ascending stroke or a letter with a descending stroke, which could occur at various within-word positions. We predicted that synesthetes should be faster and more accurate than controls, and possibly show a lesser influence of target position, due to parallel perception of whole words in their mind's eye (Figure 4.1C).

Figure 4.1

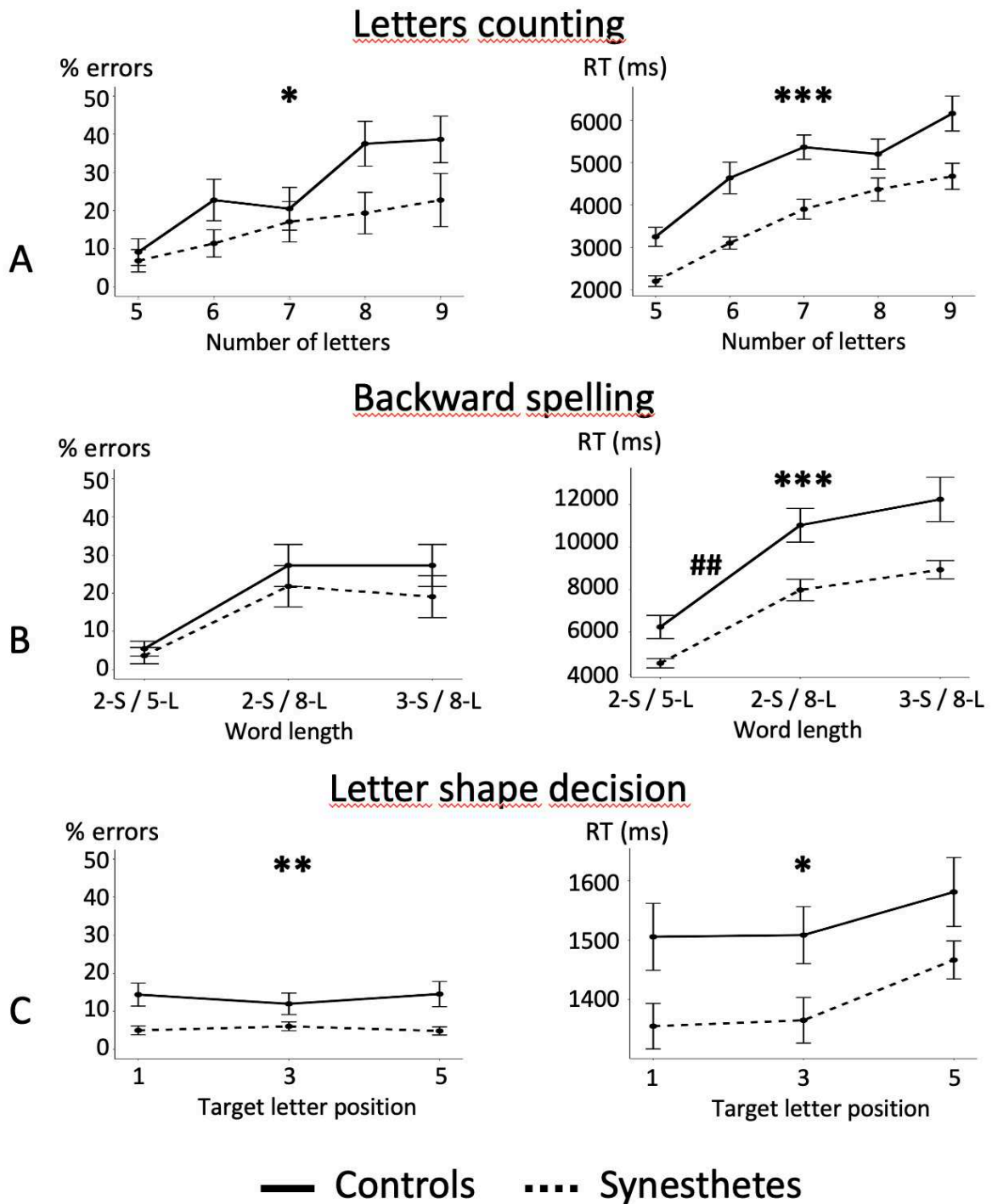


Figure 4.1

Mean error rates (left column) and response times (right column) for the 3 tasks in which we predicted an advantage for synesthetes (dotted lines) over controls (solid line). Such an advantage prevailed in all tasks. Moreover, in the backward spelling task, the effect of word

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length was smaller in synesthetes than in controls. Error bars represent +/- 1 SEM. Stars indicate the significance of the main effect of group (*: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$). Hashtags indicate the significance of the interaction of orthographic length x group (##: $p < 0.01$).

Overall, synesthetes made fewer errors than controls (5.3% vs 13.6%; $\chi^2(1)=9.09$, $p=0.003$; OR = 2.80, 95% CI 1.43 – 5.46, indicating a medium effect) and responded faster (mean correct RT: 1396 ms vs 1531 ms; $F(1,42)=6.72$, $p=0.013$, $\eta_p^2 = 0.14$, indicating a large effect). Accuracy did not vary with the position of the target letter ($\chi^2(2)=0.062$, $p < 1$), while reaction times did ($F(2,85)=3.46$, $p=0.036$, $\eta_p^2 = 0.08$ indicating a medium effect), due to longer latencies to targets in the fifth position. Still, post-hoc pairwise comparisons across positions were non-significant ($p(1-3)=1$, $p(1-5)=0.072$, $p(3-5)=0.08$, with Bonferroni correction). There was no interaction between group and target position (error rates: $\chi^2(2)=4.13$, $p=0.127$; RT: $F(2,3450)=1.03$, $p=0.358$). The Spearman-Brown corrected reliability estimate was 0.93, 95% CI [0.89 - 0.96] for accuracy, and 0.97, 95% CI [0.95 - 0.98] for RTs.

After the experiment, 21 (95%) synesthetes reported that TTS helped them with the task, while 1 reported neither an advantage nor a hindrance.

D. Interference of speech on visual lexical decision

Participants were presented visually with strings of letters and decided whether they formed a real word or a pseudoword, under interference by normal speech or continuous scrambled speech, or in silence. We predicted that, in synesthetes more than in controls, lexical decision should be impaired during TTS-inducing speech relative to scrambled speech and silence (Figure 4.2A).

Overall, synesthetes and controls did not differ in error rate (27.2% vs 27.9%; $\chi^2(1)=0.162$, $p=0.69$) nor in RT (621 ms vs 630 ms; $F(1,41)=0.037$, $p < 1$). RT differed across types of auditory background ($F(2,4645)=3.78$, $p=0.023$), due to longer latencies during silence than during auditory interference (634 ms vs 621 ms; $F(1,4698)=7.29$, $p=0.007$). Normal and scrambled speech did not differ. There was no interaction between group and type of auditory background (error rates: $\chi^2(2)=1.60$, $p=0.449$; RT: $F(2,5368)=0.316$, $p < 1$). We then compared

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responses to words and pseudowords. Participants made fewer errors (16.8% vs 38.3%; $\chi^2(1)=155$, $p<0.001$, OR = 3.58, indicating a medium effect) and responded faster (mean correct RT: 579 ms vs 687 ms; $F(1,168)=368$, $p<0.001$, $\eta_p^2 = 0.69$, indicating a large effect) with words than pseudowords. There was no interaction between lexicality and type of auditory background. Interestingly the effect of lexicality on RT was smaller in synesthetes than in controls (interaction $F(1,5300)=10.256$, $p=0.001$; Figure 4.2A, $\eta_p^2 = 0.002$, indicating a small effect), with no interaction with error rates. Post-hoc comparisons found no difference between group for either words or pseudowords separately (see Supplementary figure 4.2). The Spearman-Brown corrected reliability estimate was 0.92, 95% CI [0.88 - 0.95] for accuracy, and 0.96, 95% CI [0.94 - 0.98] for RTs.

On debriefing, 12 (55%) synesthetes reported that TTS was neither an advantage nor a hindrance in this task, 5 reported a hindrance, 3 an advantage, and 2 did not know.

Figure 4.2

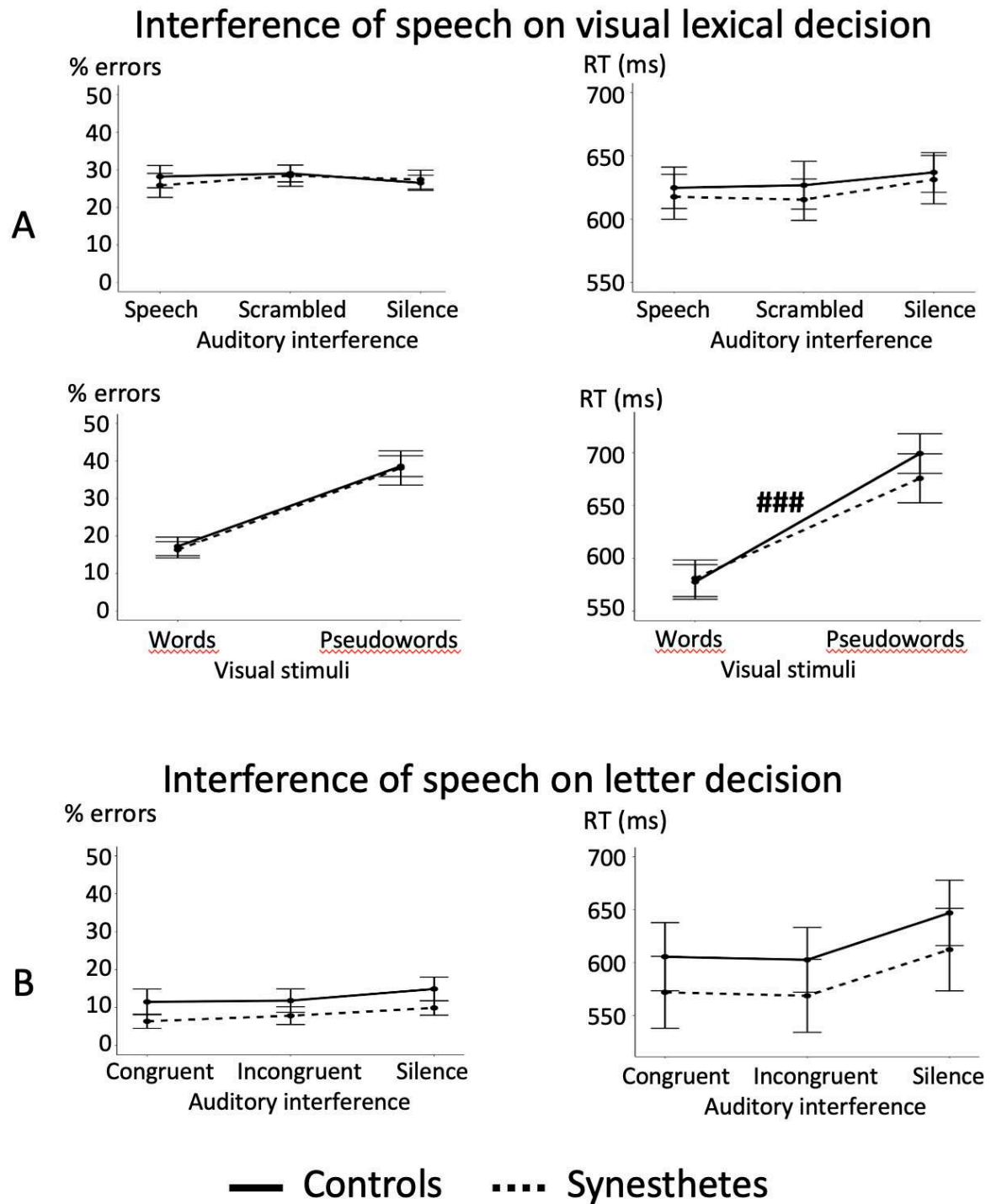


Figure 4.2

Mean error rates (left column) and response times (right column) for the 2 reading tasks in which we predicted that synesthetes (dotted lines) should show a larger interference from speech than controls (solid lines). Synesthetes did not differ from controls, except for an

interaction of lexicality x group in lexical decision (###: $p=0.001$). Error bars represent ± 1 SEM.

E. Interference of speech on letter decision

Participants had to identify a scarcely visible letter, presented under auditory interference by a repeated syllable congruent (e.g. “bababa” with B), or incongruent (e.g. “rarara” with B) with the target letter, or with no interference. We predicted that, in synesthetes more than in controls, performance on letter decision should be impaired by incongruent interference, and possibly supported by congruent interference, relative to the silent conditions eliciting no TTS (Figure 4.2B).

Overall, synesthetes and controls did not differ in error rate (8% vs 12.7%; $\chi^2(1)=0.791$, $p=0.37$) nor in RT (584 ms vs 618 ms; $F(1,42)=0.6$, $p=0.443$). The comparison of interference by congruent vs incongruent spoken syllables showed no difference in error rate ($\chi^2(1)=1.43$, $p=0.23$) or RT ($F(1,42)=0.16$, $p=0.68$), with no interaction of group x congruence. The comparison of trials with auditory interference (congruent or incongruent) vs silent control trials showed that participants were more accurate (9.4% vs 12.4%; $\chi^2(1)=14.2$, $p<0.001$) and faster (587 ms vs 629 ms; $F(1,4683)=37.2$, $p<0.001$) on trials with interference, with no interaction of group x interference. The Spearman-Brown corrected reliability estimate was 0.96, 95% CI [0.93 - 0.98] for accuracy, and 0.98, 95% CI [0.97 - 0.99] for RTs.

After the experiment, 14 (64%) synesthetes subjectively reported neither an advantage nor a hindrance by TTS, while 7 reported a hindrance, and 1 an advantage.

5. Discussion

We found a measurable advantage for synesthetes over controls in Experiments 1-3, in which such an advantage was predicted. This result was congruent with the synesthetes' introspection, as in all 3 tasks a vast majority felt that TTS was helping them. In contrast, we did not find the expected impairment in Experiments 4-5. Correspondingly, in both tasks, a majority of synesthetes did not experience any hindrance by TTS. Importantly, this dissociation between tasks demonstrates that synesthetes were not just more proficient than controls in any cognitive task, but only in those tasks for which an advantage was predicted from the unique features of TTS.

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Discussion

A. The advantage of being a synesthete

Experiments 1-3 were based on the prediction that synesthetes should show an advantage in tasks requiring some form of stable and distinctive imagery of letters, on which to perform the mental manipulations required for counting, backward spelling, and shape decision. In this context, mental imagery may be seen as a component of working memory, a cognitive space where information can be transiently stored and manipulated.

The concepts of visual working memory and mental imagery are closely related, with both behavioral (Keogh and Pearson, 2011) and imaging evidence (Albers et al., 2013) that they share some common mechanisms. Imagery, one among several possible working memory strategies, is mostly summoned by “good imagers” in visual working memory tasks (Pearson and Keogh, 2019), and high imagery vividness is positively correlated across individuals with better working memory performance (Slinn et al., 2023).

Letter counting, backward spelling, and letter shape decision are typical instances of tasks relying on working memory, with facilitation by powerful mental imagery. Most previous evidence concerns backward spelling and related paradigms. Indeed, typical subjects, when asked to spell a word backward, “invariably report using an image of the written word to ‘read off’ the letters”, while response latencies reflect the orderly scanning of the word from right to left (Hampson and Morris, 1978). There are indications that for longer words, typical subjects may segment words on the basis of phonology and scan the resulting chunks with visual mental imagery (Hampson and Morris, 1978; Service and Turpeinen, 2001). Using a similar strategy, abacus operators take advantage of their vivid imagery of the abacus to report the digit located at a probed position within a series, accurately and with little effect of serial position (Hishitani, 1990). Hence in tickertape synesthetes, exploiting the intense and effortless orthographic images seems to be the optimal and unescapable strategy, explaining their superiority to controls. Coltheart and Glick (Coltheart and Glick, 1974) reported the case of a woman, likely a type of TTS, who could easily pronounce and spell words backwards, explaining that “she could make herself see the spoken word in front of her and so could read it off easily, in either direction”. Finally, in addition to an overall advantage, synesthetes showed reduced sensibility to word length, confirming the benefit of a stable whole-word mental image. Holm et al. (2015) did not find superior backward spelling abilities in

participants with good orthographic imagery, but data were only introspective and incapable of revealing relatively subtle differences in error rate and response latency.

B. Why synesthetes did not suffer from speech interference

Experiments 4-5 were inspired by the thought that (1) responses to target visual stimuli are often influenced by task-irrelevant surrounding visual stimuli, which cannot be fully dismissed by attentional focus (Eriksen, 1995); and (2) irrelevant synesthetic words or letters should interfere with difficult perceptual decisions on actual words or letters. Thus, in lexical decision, responses are slowed down by the mere presence of irrelevant flanking words (e.g. Vandendaele and Grainger, 2022), and in letter decision, performance is degraded by the presence of flanking letters (Eriksen and Eriksen, 1974). We expected that in those two experiments synesthetic images would play the role played by flanking stimuli in such paradigms. However, this is not what we observed.

Why was performance actually better in conditions with auditory distractors, irrespective of the presence or absence of TTS, whereas a negative effect of irrelevant speech on the visual task was expected? Irrelevant meaningful speech, and to a variable extent meaningless sounds, interfere with off-line text comprehension tasks (e.g. Banbury and Berry, 1998; Martin et al., 1988), and with a variety of memory tasks (for reviews see Guerreiro and Van Gerven, 2011; Marsh and Jones, 2010). There are however few data on the effect of irrelevant speech on lower-level on-line tasks with written words or letters, such as those which we used in Experiments 4-5. LaPointe et al. (2007) found essentially no effect of speech distraction on fast decision tasks with single digits or words. In lexical decision proper, a spoken word presented simultaneously to the written target increased error rates only when target and distractor were phonologically similar (Eiter and Inhoff, 2008), which was never the case in our experiments. Moreover, in auditory attention switching and working memory tasks, Nagaraj (Nagaraj, 2021) showed that participants were actually faster in the presence of noise. On the basis of such limited evidence, one may speculate that in blocks with auditory distractors, participants focused actively their attention towards the visual stimuli, with an overshoot such that performance was actually better than during the silent condition in which visual attention was more relaxed. Such alternation of strategy was encouraged by the block structure of the lexical decision experiment. Moreover participants were explicitly instructed

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Discussion

to ignore auditory stimuli, which they successfully did. This pattern may have also been supported by the attentional dominance of the visual over the auditory modality commonly observed in bimodal settings (for a review see Spence, 2010). Finally, in the letter decision experiment, the auditory distractors provided a cue allowing participants to allocate their attention on the time window during which the visual letter appeared, thus improving performance in non-silent conditions (Naccache et al., 2002).

The lack of any interference by speech distractors also explains mechanically the lack of difference between conditions in which high vs low interference was expected (normal speech and incongruent syllables vs scrambled speech and congruent syllables).

Regarding the absence of the expected difference in performance level between synesthetes and controls, two options may be considered. First, if fully unattended speech simply does not generate TTS, then it is natural that synesthetes behaved like controls, as discussed above. Alternatively, if unattended speech does generate TTS, the lack of difference between groups would imply that the evoked synesthetic words did not interfere with the visual tasks.

We do not have conclusive data on the ability of unattended speech to generate TTS. In a group of 26 synesthetes including most of the current participants, 58% reported that unattended speech, e.g. in a restaurant, still triggered TTS (Hauw et al., 2023a). During the debriefing of both Experiments 4 and 5, although we did not formulate this question as such, only 4 synesthetes reported that they experienced no TTS. However, the introspection that unattended speech triggers TTS must be taken with caution, as attention is likely to move towards and away from surrounding speech, and reports of TTS may correspond to moments when speech was actually attended. At any rate, assuming that unattended speech does generate TTS, the lack of interference in synesthetes could result from the specifics of the on-line low-level tasks we used, as discussed above. Indeed, most synesthetes reported that synesthetic and actual letters occupied distinct mental spaces, and/or that they could effectively focus their attention on visual stimuli and discount auditory distractors.

In the lexical decision experiment, although synesthetes were not overall disadvantaged, they nevertheless differed significantly from controls by showing a smaller difference between response latencies to words and pseudowords. Although the present data are clearly insufficient to fully explain this difference, two remarks are in order. First, for instance in a

diffusion decision model (DDM) of lexical decision (Ratcliff et al., 2004), the RT difference between words and pseudowords results from respectively faster and slower accumulation of evidence, as modeled by the “drift rate” of diffusion. The group x lexicality interaction would then point to group differences in the way lexical, semantic, phonological, and orthographic information contributes to the eventual decision, for words, for pseudowords, or both. Such differences would not be surprising, construing TTS as a symptom of increased links between phonology and orthography. Second, this subtle behavioral difference between synesthetes and controls, in the order of tens of milliseconds, may not be a consequence of the subjective phenomenon which defines TTS, but rather a side effect of atypical interactions between language representations.

In order to answer those questions and gain access to the cognitive mechanisms of TTS, future behavioral studies should explore several paths. First, one may look for deleterious effects of TTS on working memory and text comprehension paradigms, as predicted from the frequent complaint of synesthetes of difficulties reading when surrounded by people talking (Hauw et al., 2023a), and from the interference of irrelevant speech with such high-level tasks in typical individuals (Banbury and Berry, 1998; Guerreiro and Van Gerven, 2011; Marsh and Jones, 2010; Martin et al., 1988). Second, the attention and conscious access to speech stimuli should be carefully controlled and manipulated, in order to understand their impact on triggering TTS, as has been done in studies of grapheme-color synesthesia (see e.g. Mattingley et al., 2001; van Leeuwen et al., 2015). Third, more refined behavioral priming and other paradigms are required to assess language information processing in synesthetes beyond the subjective TTS phenomenon. Such data will be critical for informing the emergent study of the brain mechanisms of TTS (Hauw et al., 2023c).

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In TTS, as in other synesthesias, we have shown that under certain conditions, behavioral differences can be measured. Our next objective was to identify the networks underlying TTS.

CHAPTER V

Subtitled speech: the neural mechanisms of tickertape synesthesia

Subtitled speech: the neural mechanisms of tickertape synesthesia

Fabien Hauw^{a, b}, Benoît Béranger^a, Laurent Cohen^{a, b}

Author affiliations:

a. Inserm U 1127, CNRS UMR 7225, Sorbonne Universités, Institut du Cerveau, ICM, Paris, France

b. AP-HP, Hôpital de La Pitié Salpêtrière, Fédération de Neurologie, Paris, France

1. Abstract

Reading acquisition modifies areas of the brain associated with vision, with language, and their connections. Those changes enable reciprocal translation between orthography, and word sounds and meaning. Individual variability in the pre-existing cerebral substrate contributes to the range of eventual reading abilities, extending to atypical developmental patterns, including dyslexia and reading-related synesthesias. The present study is devoted to the little-studied but highly informative tickertape synesthesia (TTS), in which speech perception triggers the vivid and irrepressible perception of words in their written form in the mind's eye. We scanned a group of 17 synesthetes and 17 matched controls with functional MRI, while they listened to spoken sentences, words, numbers, or pseudowords (Experiment 1), viewed images and written words (Experiment 2), and were at rest (Experiment 3). First, we found direct correlates of the TTS phenomenon: During speech perception, as TTS was active, synesthetes showed over-activation of left perisylvian regions supporting phonology, and of the occipitotemporal Visual Word Form Area (VWFA), where orthography is represented. Second, we brought support to the hypothesis that TTS results from atypical relationships between spoken and written language processing: The TTS-related regions overlap closely with cortices activated during reading, and the overlap of speech-related and reading-related areas is larger in synesthetes than in controls. Furthermore the regions over-

activated in TTS overlap with regions under-activated in dyslexia. Third, during resting state, in the absence of TTS, we identified putative correlates of a predisposition to synesthesia: Synesthetes showed increased functional connectivity between left prefrontal and occipital regions, a pattern that may reflect a lowered threshold for conscious perception. Those data provide a rich and coherent account of TTS as a non-detrimental developmental condition created by the interaction of reading acquisition with an atypical cerebral substrate.

2. Introduction

Reading acquisition leads to deep changes in brain areas related to vision and language, and in their connections (Dehaene et al., 2015), enabling the translation from orthography to sound and meaning during reading, and the opposite translation during spelling. Key among those changes is the emergence of a small area sharply specialized for letters recognition in the left fusiform gyrus, a region known as the Visual Word Form Area (VWFA; Cohen et al., 2000; Dehaene-Lambertz et al., 2018). The VWFA has privileged connections with language areas in the left perisylvian cortex (Bouhali et al., 2014). This enhanced anatomical and functional connectivity exists before reading acquisition (Saygin et al., 2016; Yu et al., 2022) and is further reinforced by reading acquisition (López-Barroso et al., 2020; Thiebaut de Schotten et al., 2014).

All changes associated with reading acquisition act on a preexisting cerebral substrate whose individual features, partly genetically determined, modulate reading acquisition and contribute to the eventual variability in reading skills. Such variability includes the span of typical reading, as shown by a host of twin studies and genome-wide association studies (Andreola et al., 2021; Eising et al., 2022; Hart et al., 2013). In a minority of the population, atypical brain organization is revealed through dyslexia, a variety of selective impairments in learning to read (Friedmann and Coltheart, 2018), associated with abnormal patterns of brain activation (Feng et al., 2020) and connectivity (M. Vandermosten et al., 2012).

In another few percent of children, atypical brain organization does not yield reading impairment, but unusual perceptual contents, or synesthesias, associated with written language (Ward, 2019; Ward and Simner, 2020). The present study is devoted to the little-studied but highly informative tickertape synesthesia (TTS), a condition first described by Francis Galton (1883), in which speech perception triggers the irrepressible and vivid

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Introduction

perception of words in their written form in the mind's eye (Hauw et al., 2023b, 2023a; Holm et al., 2015). The most studied synesthesia involving letters is grapheme-color synesthesia, in which each letter is perceived in association with a given color (e.g. Hubbard et al., 2005), but still other synesthesias have been reported, including the attribution to letters of well-defined gender and personality traits (see www.thesynesthesiatree.com).

TTS is the only synesthesia in which both the “inducer” and the “concurrent” are in the realm of language, respectively phonological and orthographic representations. Indeed, auditory stimuli trigger TTS in as much as they can be phonologically coded: real words with regular or irregular orthography, pseudowords, unfamiliar languages with a familiar phonology, and even natural sounds with a conventional onomatopoeic transcription (Hauw et al., 2023a). This implies that the strings of letters which materialize in the mental imagery of synesthetes are derived from speech through the two usual routes which operate during reading: a phonological route implementing phoneme-grapheme correspondences, and a lexical route retrieving stored word spelling (Coltheart, 2012; Hauw et al., 2023a). We therefore propose that TTS reflects exceptionally powerful and automatic top-down influences from perisylvian speech areas, in which phonology is processed, onto the VWFA which supports orthographic representations.

A group of 17 tickertape synesthetes and matched controls were scanned with fMRI while they listened to speech (Experiment 1), viewed written words and other images (Experiment 2), and were at rest (Experiment 3). This paradigm aimed at assessing the following set of predictions.

As TTS consists in the vivid perception of letters generated from sound, our first prediction was that speech perception should activate perisylvian language areas involved in speech processing and phonology-to-orthography translation, and VOT regions subtending orthography, i.e. the VWFA. As we previously observed that TTS was triggered by any auditory input provided that it has phonological content, our second prediction was that TTS-related activations should equally occur while synesthetes are listening to real or pseudo-words (Hauw et al., 2023a). Thus considering TTS as a kind of upended reading process, our third prediction was that regions involved in TTS should overlap with those associated with reading and dyslexia. Finally, our fourth and less specific expectation was that the pattern of

connectivity during rest may reveal underlying predispositions to TTS (and possibly to other associated synesthesias), measurable even in the absence of speech perception.

3. Materials and Methods

A. Participants

We created a short description of TTS, and recruited participants by broadcasting it through email and social networks, targeting particularly groups of students and university members, and groups devoted to synesthesia, psychology, and neuroscience. We thus recruited 22 tickertape synesthetes, plus 22 controls matched one-to-one to synesthetes based on age, gender, education level and handedness. We excluded 5 left-handed participants in each group, resulting in 2 groups of 17 participants. All participants were native French speakers, right-handed according to the Edinburgh Inventory (Oldfield, 1971), had normal or corrected-to-normal vision and hearing, and had no history of neurological or psychiatric disorders. They were a subset of the participants in a behavioral study of TTS (Hauw et al., 2023b). The research was approved by the institutional review board of the INSERM (protocol C13-41), and all participants provided informed written consent in accordance with the Declaration of Helsinki.

B. MRI acquisition and preprocessing

All images were acquired on a Siemens 3T MAGNETOM Prisma scanner. T1-weighted anatomical images (TR/TE/flip angle = 2400 ms / 2.23 ms / 9°, voxel size = 0.7 × 0.7 × 0.7 mm) were acquired with a 64-channel receive-only head coil. For functional images, we used multi-echo fMRI sequences (Posse, 2012) : time repetition (TR) = 1660 ms; multi-time echo (TE) = 14.2, 35.39, 56.58 ms; flip angle = 74°; voxel size = 2.5 × 2.5 × 2.5 mm; 60 slices; 20-channel receive-only head coil. Cardiac and breathing frequencies were recorded using a pneumatic breathing belt and a pulse oximetry unit.

Using CAT12 (<http://www.neuro.uni-jena.de/cat>), anatomical volumes were segmented, normalized to the standard MNI stereotactic space and resampled to 1.5 x 1.5 x 1.5 mm. Functional images were processed as follows. Using `afni_proc.py`, all echoes time-series were despiked and slice-time corrected. Motion correction was computed on the first echo with the

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volume with the lowest motion as reference, then applied to all echoes, and finally merged using optimal combination `t2smmap.py` (see `meica.py` provided with AFNI: <http://afni.nimh.nih.gov/afni/>). Finally, using SPM12 (Wellcome Institute of Imaging Neuroscience, London, UK) implemented in Matlab, functional time-series were co-registered to the anatomical volume, then normalized to Montreal Neurological Institute (MNI)-space (2.5mm isotropic), and spatially smoothed (5mm full-width at half-maximum [FWHM] isotropic).

C. Experiment 1: fMRI study of speech perception

i. Stimuli and procedure

The stimuli consisted of spoken pseudowords, words, numbers, sentences and scrambled sentences, presented in a block design, with interspersed blank periods, in random order. Auditory words and pseudowords were a subset of those used in Bouhali et al. (2019). Words and pseudowords ranged from 5 to 10 letters, and from 1 to 3 syllables. Numbers ranged from 1 to 4 syllables and did not significantly differ in length from words. The sentences were consecutive fragments of the Snow-White tale. All stimuli were generated using the `ttsreader.com` speech generation software with a female voice. These four conditions will be subsequently referred to as the speech conditions. Scrambled stimuli were derived from the sentences using an algorithm preserving the spectral content over long time scales while removing structures at shorter timescales (www.mathworks.com/matlabcentral/fileexchange/29396-time-domain-scrambling-of-audio-signals (Ellis, Dan, 2023)). The experiment lasted 13.4 minutes. To optimize the design for multivariate pattern analysis (MVPA), we divided the experiment in 8 blocks of 1.3 minutes each, separated with 15 s silent periods. Each block consisted of 5 mini-blocks, one for each type of stimuli, separated with 3 s silent periods. Moreover the experiment started and ended with a 15 s silence. Participant had to detect the occasional target pseudoword “tatatata”, occurring once randomly in half the mini-blocks, pronounced by the same voice as stimuli. Stimuli were presented using Psychtoolbox v3 in MATLAB (Mathworks, Natick, MA, USA).

ii. Statistical analysis

For single-subject analyses, we defined a general linear-model (GLM), with regressors for all experimental condition (words, pseudowords, sentences, scrambled sentences, numbers), plus a regressor for targets and one for motor responses. Those regressors were created by convolving boxcar functions based on the onsets and durations of events with a canonical hemodynamic response function (HRF). The GLM also included 24 motion parameters, and regressors modeling physiological noise derived from cardiac and respiratory activity (TAPAS toolbox, <https://github.com/translationalneuromodeling/tapas>); Time-series were high-pass filtered (128 s cutoff). Individual contrast images of each of the 5 conditions vs baseline were smoothed (8mm FWHM) and entered in a second-level ANOVA with subject as random factor, group as between-subjects factor and conditions as within-subjects factor. Unless stated otherwise, the statistical threshold was set to $p < 0.001$ for the voxel-wise threshold, and to $p < 0.05$ for the cluster-wise threshold FWE-corrected for multiple comparisons across the whole brain.

iii. Definition of individual ROIs

Based on activations in Experiment 1, we defined individual regions of interest (ROIs) for use in functional connectivity analyses. For each participant, we created 9 ROIs, defined as 4 mm-radius spheres. Those spheres were centered on the participant's voxel most activated (highest t-value) by the contrast speech > baseline within a 6 mm-radius sphere centered on the main peaks of the "TTS network", defined by the group-level contrast (speech > baseline) x (synesthetes > controls) (see Results). These 9 ROIs were used as seeds for the analysis of resting-state data. We created a second set of 9 ROIs for each subject, using the same method, except that participants' most activated voxel was identified using the contrast sentences > scrambled sentences. These ROIs were used as seeds in psychophysiological interaction (PPI) analyses.

iv. Psychophysiological interaction (PPI) analysis

Our aim was to study condition-dependent changes in the functional connectivity between specific seeds and the rest of the brain, and to compare those changes between groups.

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Specifically, we compared connectivity during speech vs baseline, and during sentences vs scrambled sentences. We used the default SPM12 PPI method. For each participant, each pair of compared conditions, and each seed ROI (see above), we computed a contrast image comparing the correlation map of the seed with the rest of the brain during the two compared conditions. Those first-level images were smoothed (FWHM 8 mm) and entered in second-level ANOVAs, one for each pair of compared conditions, with subject as random factor, group as between-subjects factor and ROIs as within-subject factor. The statistical threshold was set to $p < 0.001$ for the voxel-wise threshold, and to $p < 0.05$ for the cluster-wise threshold FWE-corrected for multiple comparisons across the whole brain.

v. Multivariate pattern analysis (MVPA)

We used The Decoding Toolbox (Hebart et al., 2015), in order to decode words from each of the other conditions based on multivoxel activation patterns. We applied a leave-one-block-out cross-validation design across the 8 blocks of the experiment. Decoding was performed across the whole brain, with a 10 mm-radius searchlight. Decoding performance around each voxel was quantified as the accuracy above the 0.5 chance level. Individual accuracy maps were then smoothed (8mm FWHM) and entered in two-sample t-tests. The statistical threshold was set to $p < 0.001$ for the voxel-wise threshold, and to $p < 0.05$ for the cluster-wise threshold FWE-corrected for multiple comparisons across the whole brain.

D. Experiment 2: fMRI study of word reading

i. Stimuli and procedure

The stimuli consisted of printed words, Arabic numbers, pictures of houses, faces and tools, presented in a block design, with interspersed blank periods, in a random order. Words ranged from 3 to 5 letters (mean=4.8). Numbers were matched to the words in orthographic length. Houses, faces and tools were black and white pictures. Luminance and contrast did not differ across categories. Stimuli were displayed in the center of a grey circle on a black background. The experiment was divided in 8 blocks, of 1.6 minutes each, separated with a 15 s silent period. Each block consisted of 10 mini-blocks, i.e. 2 mini-blocks for each condition, separated with a 3 s silent period. Moreover the experiment started and ended with a 15 s silence. Subjects had to detect the visual target “#####”, occurring once randomly in half the mini-

blocks. The experiment lasted 15.8 minutes. Stimuli were presented using Psychtoolbox v3 in MATLAB (Mathworks, Natick, MA, USA).

ii. Statistical analysis

We used the same methods as in Experiment 1, except that the factors of interest now corresponded to the 5 types of visual stimuli.

E. Experiment 3: Functional connectivity during rest

i. Procedure

During 10 minutes, participants had to fixate a central white cross on a black screen, while the room was in darkness.

ii. Preprocessing

Images were first processed through the same general pipeline as Experiments 1 and 2. Then, applying the default settings of the Functional Connectivity Toolbox (CONN) (Whitfield-Gabrieli and Nieto-Castanon, 2012), the signal from the white matter and CSF was regressed out, and a linear detrending and a band-pass filter of 0.008–0.09 Hz were applied.

iii. Statistical analysis

Analyses were performed with the CONN toolbox. Single-subject analyses included the same regressors for motion and physiological noise as in Experiments 1 and 2. We performed ROI-to-voxel analyses using ROIs derived from Experiment 1, and voxel-to-voxel analysis of Global Correlation. The statistical threshold was set to $p < 0.005$ for the voxel-wise threshold, and to $p < 0.05$ for the cluster-wise threshold FWE-corrected for multiple comparisons across the whole brain.

4. Results

A. Experiment 1: fMRI study of speech perception

The aim of this experiment was to compare brain activation during conditions eliciting TTS and in control conditions. Participants were presented with an alternation of short auditory blocks of sentences; lists of words, pseudowords or numbers; scrambled sentences; and rest.

Activation by speech. We first averaged all conditions triggering TTS, i.e. all conditions except scrambled sentences, and compared them to baseline (Figure 5.1). Averaging across both groups, speech activated a broad left-predominant fronto-parieto-temporal network covering the usual language areas, and extending ventrally to the fusiform gyrus in the left hemisphere. We then contrasted synesthetes minus controls, masking by activation in synesthetes relative to baseline (voxelwise $p < 0.001$). Synesthetes had stronger activation (i) in the left-hemispheric VOT/VWFA (MNI -45 -51 -10; $Z=6.22$), SMG (MNI -48 -44 23; $Z=5.30$) extending to the IPS (MNI -40 -41 46; $Z=4.50$), and precentral cortex (MNI -50 -16 50; $Z=5.92$) extending to the posterior MTG (MNI -50 6 53; $Z=5.56$); and (ii) in bilateral STG/STS (left: posterior, MNI -70 -28 3; $Z>8$; middle MNI -68 -11 -2; $Z=5.99$; anterior, MNI -60 12 -7; $Z=7.59$; right: MNI 50 -24 16; $Z=6.67$; MNI 65 4 0; $Z=7.43$). For simplicity, this set of areas will be referred to as “the TTS network”. The converse contrast showed no stronger activation in controls than in synesthetes.

Comparisons between types of speech. We then compared the 4 speech conditions among them: words vs pseudowords, words vs sentences, and words vs numbers. We used univariate contrasts and multivariate pattern analysis decoding (MVPA). Averaging both groups, as expected, we found significant differences between conditions (see Supplementary figures 5.1 and 5.2). Note in particular significant decoding of words from pseudowords in a temporoparietal region overlapping with both the SMG and the posterior MTG components of the TTS network (Supplementary figure 5.2, bottom panel). Importantly, for all those analyses, we found no significant differences between synesthetes and controls. This indicates that apart from synesthesia, speech processing did not differ between the two groups. Moreover, the lack of group difference in the univariate and multivariate lexicality effects is consistent with the observation that both words and pseudowords trigger TTS (Hauw et al., 2023a).

Figure 5.1

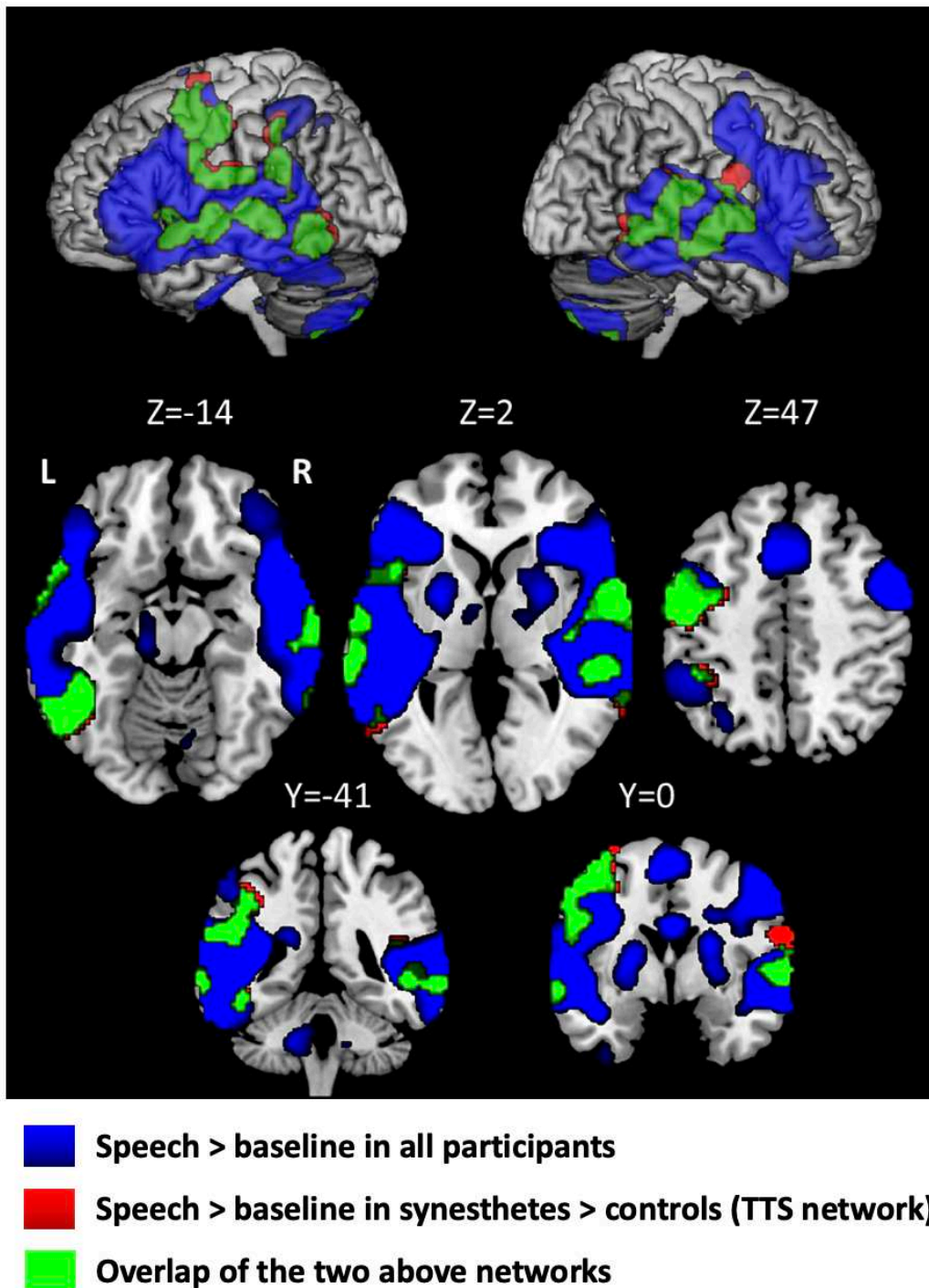


Figure 5.1

Experiment 1. Activation by speech > baseline in all participants (blue), in synesthetes more than in controls (red), and the overlap of those two volumes (green). A set of left-

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predominant regions, the “TTS network”, in the frontal, parietal and temporal lobes, were more activated in synesthetes than in controls.

Contrasting sentences and scrambled sentences. We then assessed the minimal contrast of sentences minus scrambled sentences. Averaging both groups, we found an extensive bilateral fronto-parieto-temporal network covering language areas. We contrasted synesthetes minus controls, masking by activation in synesthetes (voxelwise $p < 0.001$). We found no significant difference between groups, still with a left SMG cluster (MNI -58 -41 23; $Z = 4.36$; 99 voxels, clusterwise $p\text{-FEW} = 0.21$) and a right STS cluster (MNI 50 -34 3; $Z = 4.22$; 103 voxels, clusterwise $p\text{-FEW} = 0.248$). Both those clusters reached significance when performing the second-level analysis without smoothing input images (left SMG: MNI -60 -41 23, $Z = 4.78$; right STS: MNI 50 -34 3, $Z = 5.01$), suggesting that their lack of significance did not result from their weakness but from their intrinsically small size.

Considering that the lack of significance could also result from individual variability in the location of small activation foci, we extracted the average contrast value in the 10% best voxels of each participant, in 10-mm-radius spheres centered on the 6 main left-hemispheric peaks of the contrast of sentences minus scrambled sentences averaged over both groups. The sentences > scrambled difference was larger in synesthetes than in controls in the left SMG ($t(32) = 2.20$, $p = 0.035$) and IFG ($t(32) = 2.85$, $p = 0.008$).

Overlap of the TTS network with regions involved in dyslexia. TTS and dyslexia both result from atypical development of the cerebral reading system. In order to determine whether common areas are involved in both cases, we referred to 4 meta-analyses of imaging studies, showing reproducible areas of reduced activation in dyslexia (Linkersdörfer et al., 2012; Maisog et al., 2008; Richlan et al., 2011, 2009). Following Feng et al.’s method (Feng et al., 2020), we collected 30 left-hemispheric coordinates from those meta-analyses, and averaged nearby coordinates to create 10 8-mm-radius spherical ROIs (Supplementary table 5.1). There was a striking overlap between those ROIs and the TTS network (Figure 5.2). Within each ROI, we assessed whether the average activation by speech > baseline was larger in synesthetes than in controls. This was the case for the ITG and fusiform ROIs close to the usual peak of the VWFA (L. Cohen et al., 2002) (MNI -50 -60 -9, FDR-corrected $p < 0.001$; MNI -44 -46 -18, FDR-corrected $p = 0.003$), for nearby SMG and posterior STG ROIs (MNI -49 -44 35, FDR-corrected $p = 0.015$; MNI -52 -43 21, FDR-corrected $p < 0.001$), and for the posterior MTG ROI (MNI -54 -

51 5, FDR-corrected $p=0.035$). Note that even non-significant ROIs were partially overlapping with or contiguous to the TTS network.

Figure 5.2

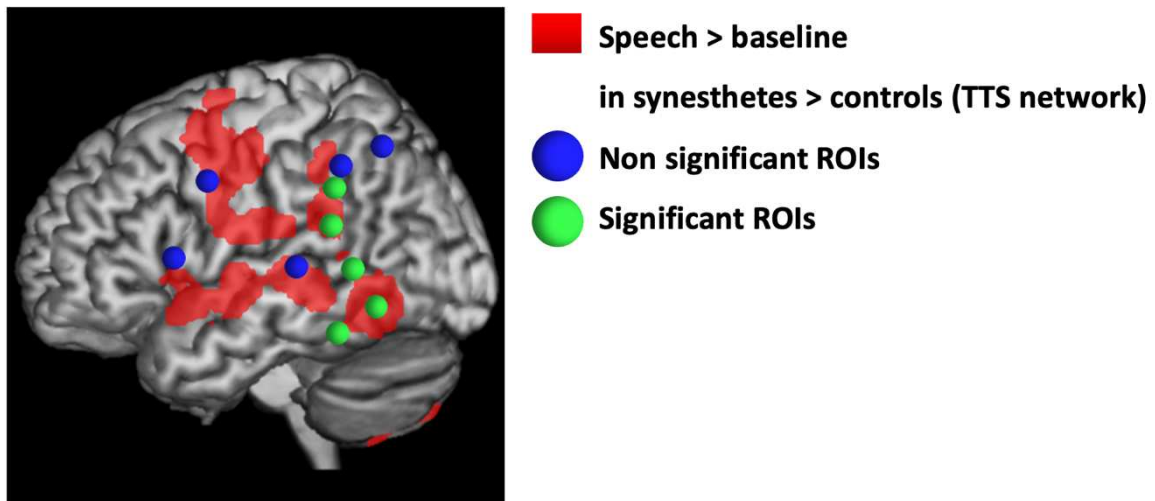


Figure 5.2

Experiment 1. Overlap of the TTS network (red) with regions of interest involved in dyslexia (centered on the spheres). Activation by speech was stronger in synesthetes than in controls in parietotemporal ROIs (green). Although not significant the other ROIs were also contiguous to the TTS network (blue).

B. Psychophysiological interaction

We then moved to analyses of functional connectivity. We reasoned that, during speech perception in synesthetes, the TTS network may not only have abnormally intense activation, as shown before, but also abnormally high connectivity, intrinsically or with other regions. We used psychophysiological interaction (PPI) to identify such regions: for each of the 9 ROIs of the TTS network, we looked for voxels whose increase in connectivity with the ROI during speech perception vs baseline would be larger in synesthetes than in controls. To limit the analysis to areas activated by speech, the analysis was masked with the volume activated by speech perception minus baseline in synesthetes (voxelwise $p<0.001$). Only the VWFA showed increased speech-dependent connectivity in synesthetes, specifically with the bilateral

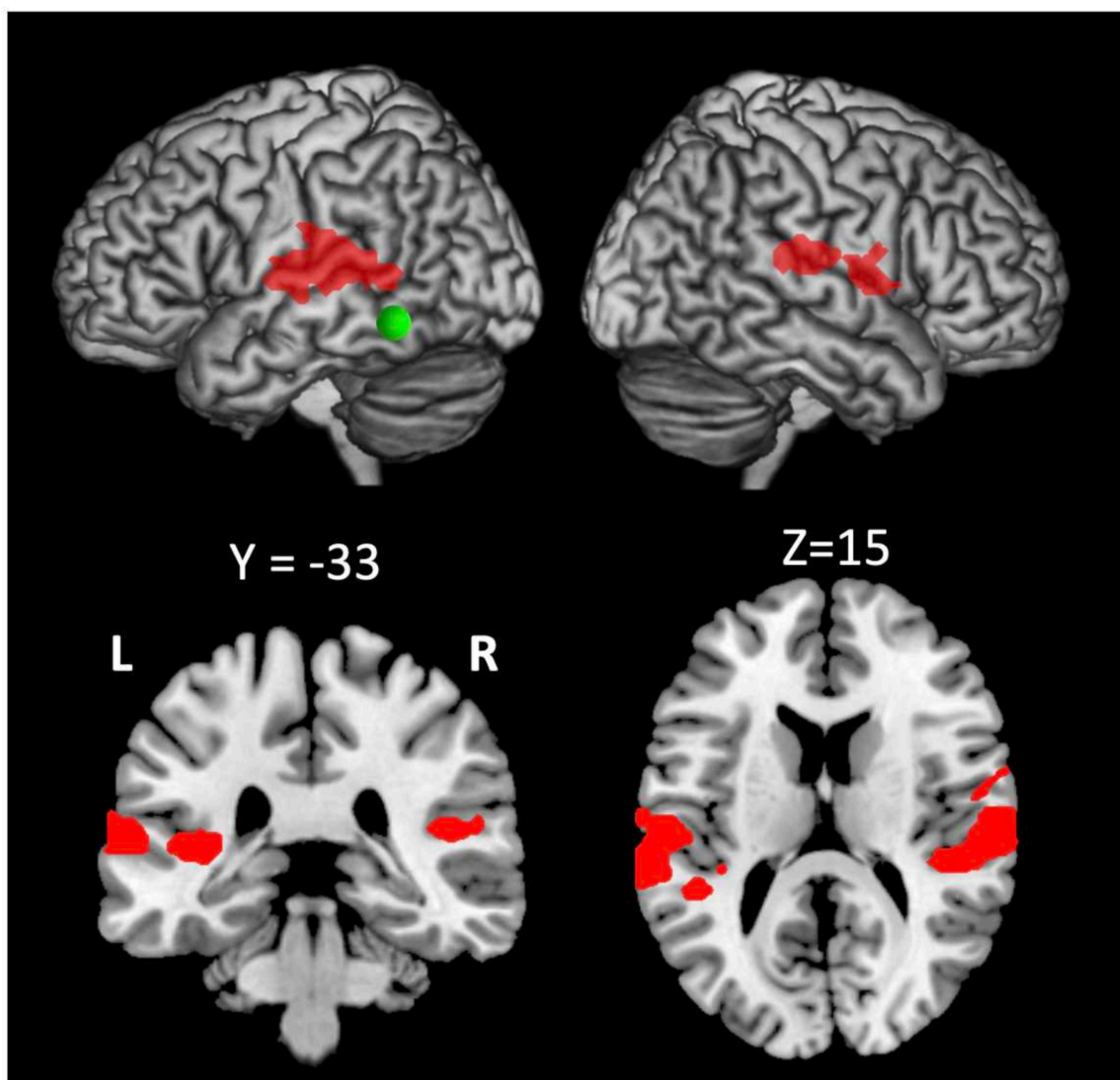
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posterior STG/SMG (Figure 5.3; left: MNI -68 -36 13, Z=4.33; right: MNI 65 6 8, Z=4.79; MNI 65 -18 20, Z=4.78). No ROI showed increased connectivity in controls relative to synesthetes.

We also compared the connectivity for the sentences > scrambled sentences contrast, masking the analysis with the volume activated by sentences perception minus baseline in synesthetes (voxelwise $p < 0.001$). No ROI showed increased connectivity in controls relative to synesthetes or conversely.

Figure 5.3



■ Regions with increased connectivity with the VWFA during speech > baseline in synesthetes > controls

● VWFA

Figure 5.3

Experiment 1. Psychophysiological interaction (PPI) analysis of the TTS network. During speech perception, the VWFA (centered on the green sphere) showed increased connectivity with left-predominant posterior STG/SMG cortex (red).

C. Experiment 2: fMRI study of word reading

The aim of this experiment was to delineate the set of regions involved in word reading, in order to then study its commonalities with the TTS network. Participants were presented with an alternation of short visual blocks of words, faces, houses, tools, and numbers.

Reading-related activations. In order to identify reading-related activations, we contrasted words minus the averaged faces, houses, and tools. Across both groups, words activated a broad network of strongly left-lateralized fronto-temporo-parieto-occipital areas, including the VWFA (in all participants: MNI -50 -54 -14, $Z > 8$; Supplementary figure 5.3; in synesthetes: MNI -50 -56 -12, $Z = 6.78$; Figure 5.4). There was no significant difference between groups. The simple contrast of words minus baseline did not differ between groups either.

Figure 5.4

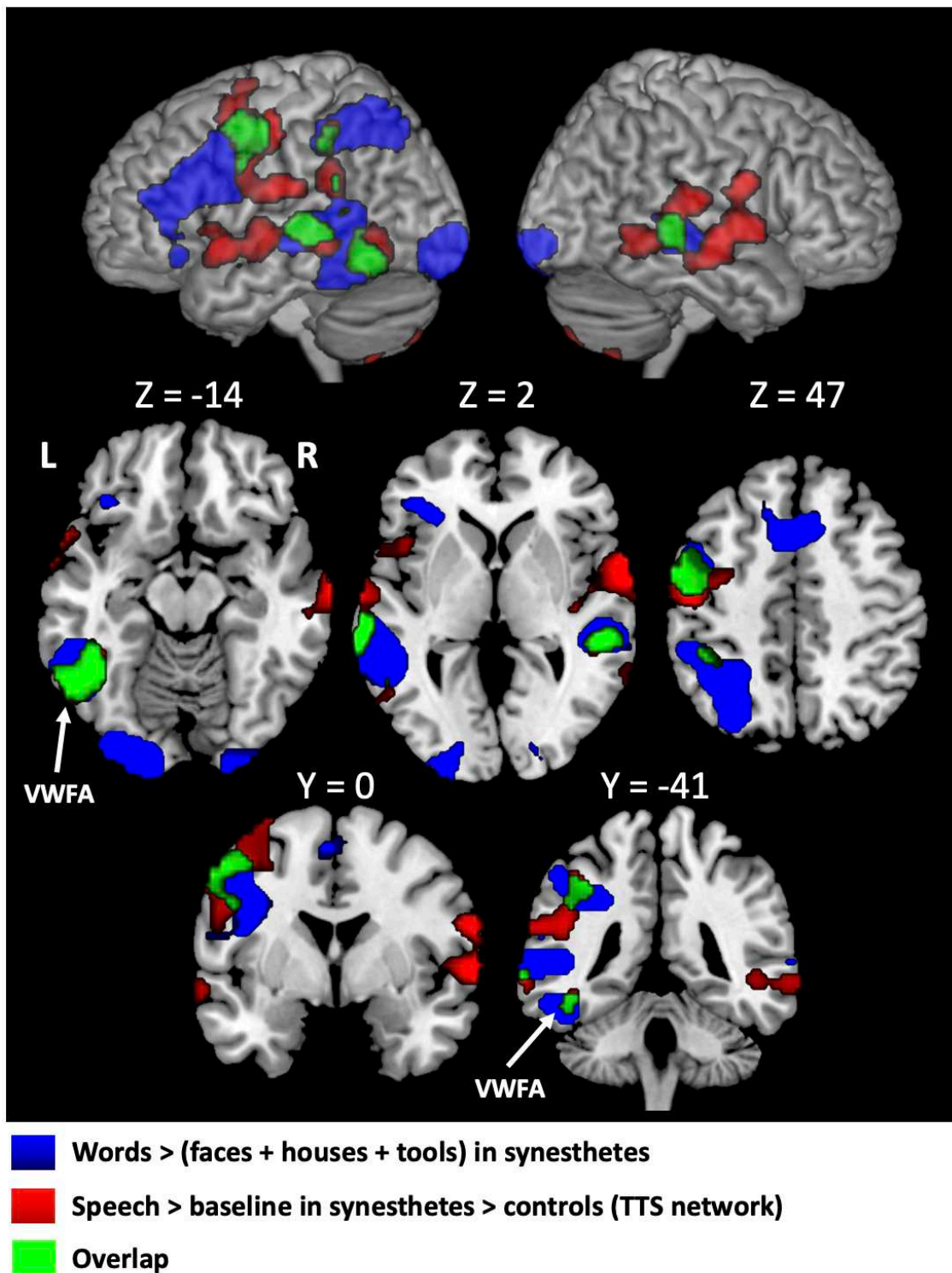


Figure 5.4

Experiment 2. Reading-related activation in synesthetes, identified by contrasting words minus faces houses and tools (blue), including the Visual Word Form Area (VWFA, white

arrows). This activation overlapped largely (green) with the TTS network as identified in Experiment 1 (red).

Other category-specific activations. We identified other category-specific activations by separately contrasting faces, houses, and tools each minus the other conditions including words. We also contrasted words vs numbers. We found the usual VOTc mosaic (Supplementary figure 5.3) comprising the bilateral LOC for tools and PPA for houses, and the right-hemispheric FFA and OFA for faces, plus stronger activation for words than numbers in the left hemisphere. None of those contrasts differed between synesthetes and controls.

D. Overlap of speech processing and word reading areas

There was substantial overlap between regions more activated during speech perception in synesthetes than in controls (i.e. the TTS network), and the reading network (Figure 5.4). This was true for all components of the TTS network: the left VWFA, SMG/IPS, prefrontal cortex, and the bilateral lateral temporal cortex. Such overlap fitted the hypothesis that, in synesthetes, speech processing is particularly entangled with reading. Hence we predicted that the overlap of the two systems should be larger in synesthetes than in controls.

To assess this prediction, we delineated in each participant the volumes activated by speech minus baseline (V_s) and by word reading minus faces, houses and tools (V_r), at 5 selection thresholds ranging from voxelwise $p < 0.05$ to $p < 0.0001$. None of those networks differed in size between synesthetes and controls, for any of the selection thresholds. We then computed the individual size of the overlap between the reading network and the speech > baseline network ($V_s \cap V_r$) (Figure 5.5, left column). The overlap was significantly larger in synesthetes than in controls, for all selection thresholds from 0.05 to 0.0001 (all $p < 0.033$). Moreover, we normalized the size of the overlap by computing Jaccard's coefficient ($[V_s \cap V_r] / [V_s \cup V_r]$). Jaccard's coefficient was larger in synesthetes only for the $p < 0.05$ threshold ($p = 0.045$). This weaker difference could be due to the vast number of parasitic sources of individual variability in the speech network, including all levels of processing involved in the 4 types of speech stimuli, ranging from acoustic and phonetic up to lexical and syntactic, and including potential influences of numbers and pseudowords.

Figure 5.5

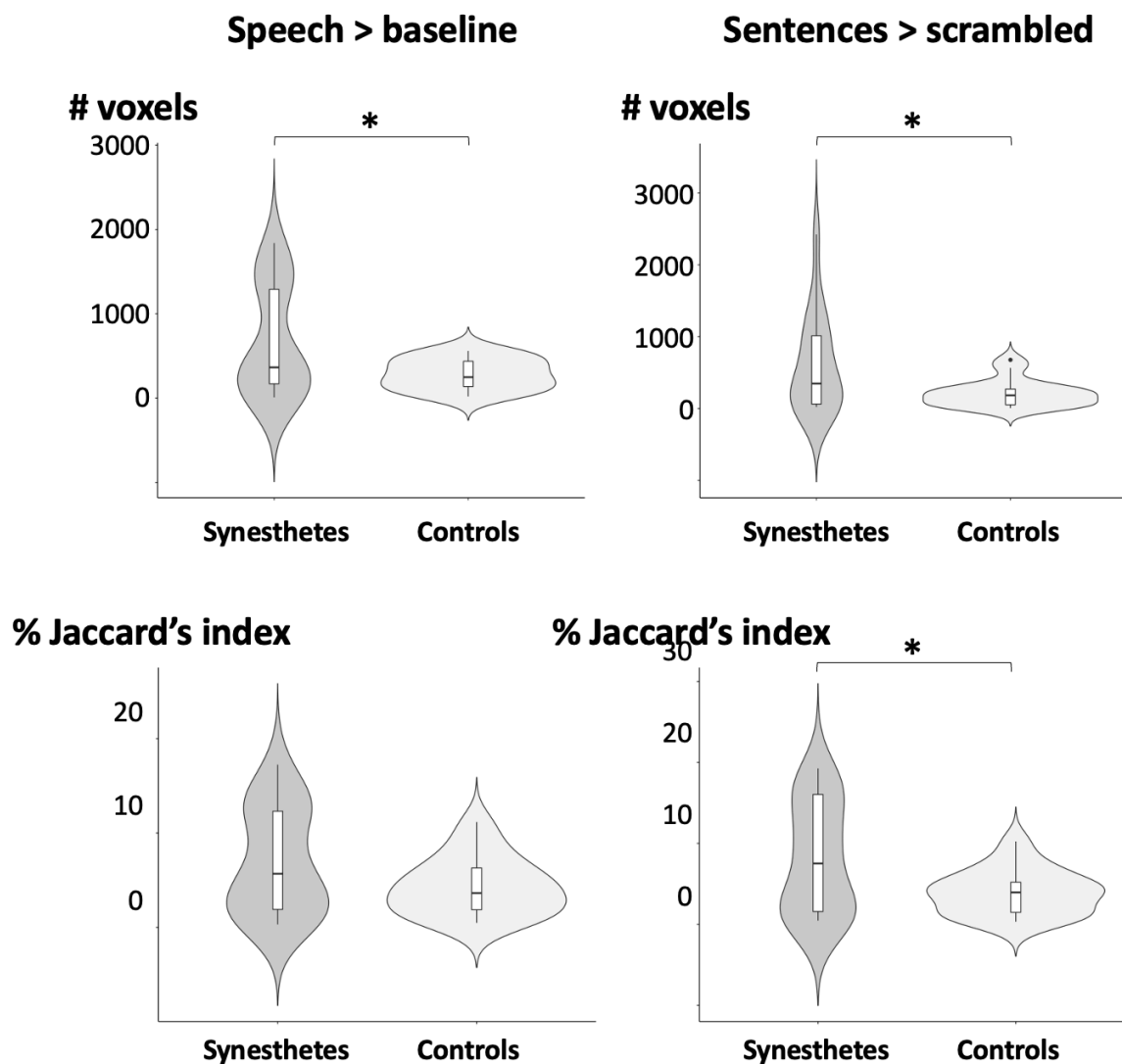


Figure 5.5

Individual overlap of speech perception activation (Experiment 1) with reading activation (Experiment 2), thresholded at voxelwise $p < 0.001$. Speech perception was defined by the contrast of speech > baseline (left column) and normal > scrambled sentences (right column). The overlap was defined in number of voxels (top row) or Jaccard's index (bottom row).

We therefore turned to the more tightly controlled definition of speech-related activations, now using the contrast of sentences minus scrambled sentences to compute Vs. Following the same method as before, we identified the activated volume in each participant, and observed

that it did not differ in size between synesthetes and controls, for any of the selection thresholds. We then computed its raw and normalized overlap with the reading network (Figure 5.5, right column). The size of the overlap was significantly larger in synesthetes than in controls for all selection thresholds from 0.01 to 0.0001 (all $p < 0.030$). Jaccard's coefficient was larger in synesthetes for all thresholds from 0.05 to 0.0001 (all $p < 0.045$).

E. Experiment 3: Functional connectivity during rest

In this experiment we studied the spontaneous fluctuation of BOLD signal during rest in order to determine whether, even in the absence of TTS, synesthetes would show a distinctive pattern of functional connectivity.

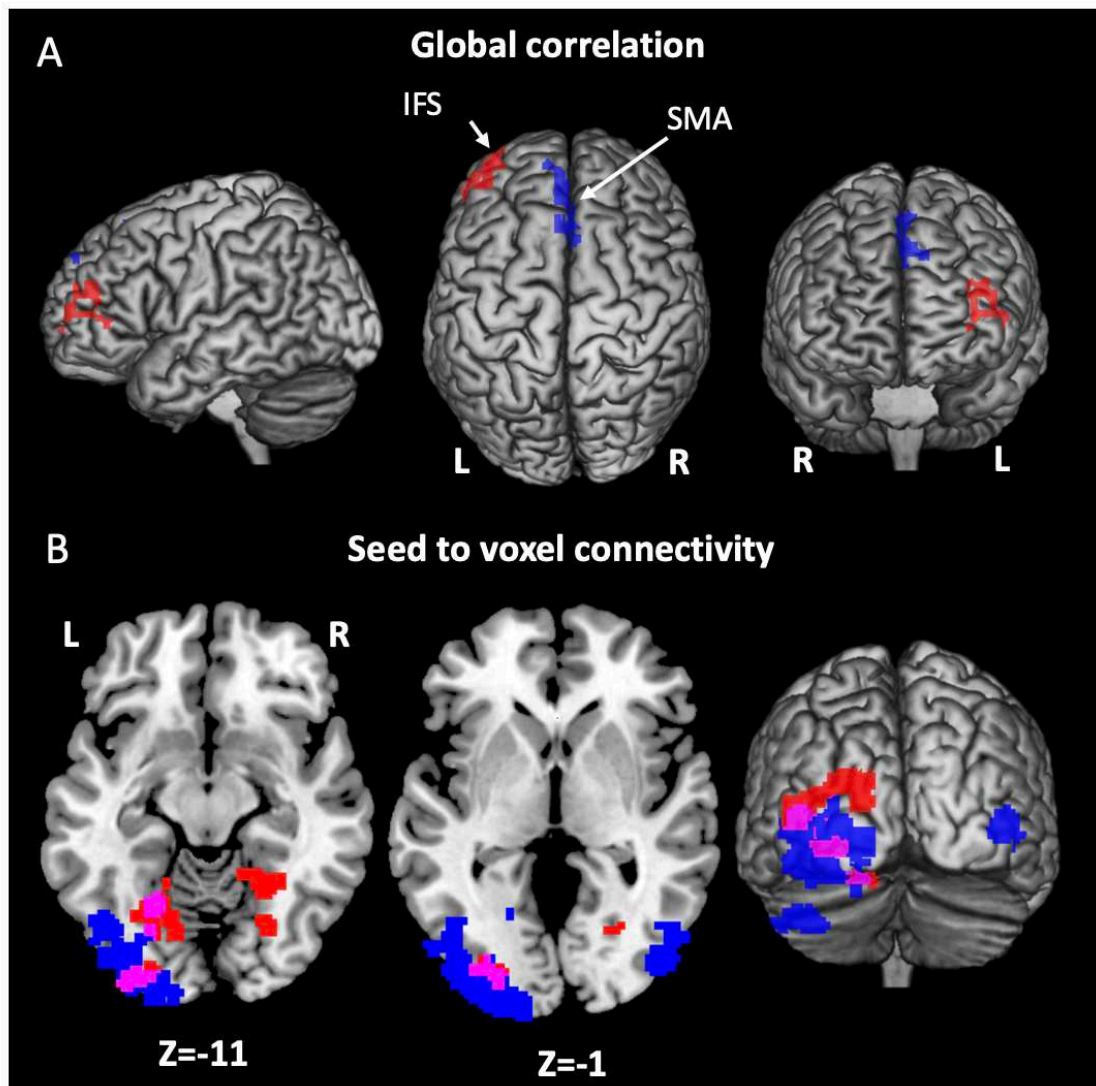
i. Global Correlation

First, we looked for brain regions more connected to the rest of the brain in synesthetes than in controls, potentially playing a role in generating synesthesia. To this end we computed for each participant a map of Global Correlation (GC), that is for each voxel the average of its correlation with all the other voxels. Two regions showed higher GC in synesthetes than in controls (Figure 5.6A): the left anterior inferior frontal sulcus (IFS) (MNI -42 46 20, $Z=3.99$) and the bilateral pre-supplementary motor area (pre-SMA; MNI 6 24 40, $Z=3.95$).

Pooling synesthetes and controls, those two regions had a similar pattern of bilateral connectivity with the lateral and mesial prefrontal cortex and the inferior parietal lobule; the middle and inferior temporal gyri for the pre-SMA and IFS seeds respectively; plus the occipital poles for the IFS seed (Supplementary figure 5.4). Apart from the occipital clusters, those regions correspond to the so-called executive or frontoparietal resting state networks (Wig, 2017).

We then assessed specifically to what areas the IFS and pre-SMA clusters were over-connected in synesthetes (Figure 5.6B). Using the IFS as seed, we found increased connectivity with the left lateral occipital cortex (MNI -42 -86 10, $Z=3.96$) and the bilateral collateral sulcus between about $Y=-70$ and $Y=-50$ (MNI 16 -46 -8, $Z=3.97$; MNI -24 -64 -10, $Z=3.63$). Using the pre-SMA as seed, we found bilateral occipital clusters (left: MNI -34 -96 -10, $Z=4.12$; right: MNI 46 -82 -2, $Z=3.92$).

Figure 5.6



- SMA (top row) and regions more connected in synesthetes than in controls (bottom row)
- IFS (top row) and regions more connected in synesthetes than in controls (bottom row)

Figure 5.6

Experiment 3. Resting state connectivity. (A) Left pre-SMA (blue) and IFS (red) with higher global correlation in synesthetes than in controls. (B) Occipital regions more correlated to the pre-SMA (blue), the IFS (red), or both (purple) in synesthetes than in controls.

ii. Connectivity of the TTS network during rest

We then looked for regions whose connectivity during rest with the 9 ROIs sampling the TTS network would differ between synesthetes and controls ($p < 0.001$ voxelwise threshold, and $p < 0.05$ clusterwise FWE-corrected threshold) (Figure 5.7 and Table 5.1). Five out of 9 ROIs showed stronger connectivity in synesthetes with left or bilateral regions: all STG ROIs (except the right anterior ROI) with the left ventrolateral and bilateral mesial occipital cortex, the right posterior STG ROI with the left temporal pole, left posterior STS/MTG and the bilateral mesial temporal. Finally, the VWFA was more connected to the bilateral postcentral sulcus, and the left precentral ROI to the bilateral mesial PFC.

Table 5.1.

<i>Seed</i>	<i>Synesthetes > Controls</i>			<i>Controls > Synesthetes</i>		
	REGIONS	MNI	Z	REGIONS	MNI	Z
<i>L posterior STG</i>	L mesial occipital	-4 -82 0	4.18	-	-	-
	L mesial occipital	-12 -106 10	4.48	-	-	-
<i>L anterior STG</i>	L ventrolateral occipital	-38 -86 -18	3.72	R ventral PFC	48 38 -18	4.02
	R mesial occipital	2 -88 20	3.51	-	-	-
	L temporal pole	-24 -2 -22	4.54	-	-	-
<i>R posterior STG</i>	L posterior STS / MTG	-70 -32 0	4.40	-	-	-
	L mesial temporal	-22 -36 -18	4.19	-	-	-
	L ventrolateral occipital	-40 -82 -14	4.16	-	-	-
<i>VWFA</i>	R mesial temporal	-30 -38 -20	4.04	-	-	-
	L postcentral sulcus	-42 -22 36	3.82	-	-	-
<i>L SMG</i>	R postcentral sulcus	66 -12 36	3.57	-	-	-
	-	-	-	R SMG / STS	70 -34 20	3.85
<i>L precentral</i>	Bilateral mesial PFC	8 46 26	3.93	-	-	-

Table 5.1. Experiment 3. Regions with different connectivity to the TTS network in synesthetes and in controls.

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L, Left; R, Right; VWFA, visual word form area; SMG, supra-marginal gyrus; STG, supra-temporal gyrus; sulcus; PFC, pre-frontal cortex; STS, superior temporal sulcus.

Voxelwise threshold $p < 0.005$, clusterwise threshold $p < 0.05$ corrected over the whole brain.

Only two ROIs showed a superiority in controls, with right-hemispheric regions: the left anterior STG with the right ventral PFC, and the left SMG ROI with the right SMG and STS.

Figure 5.7

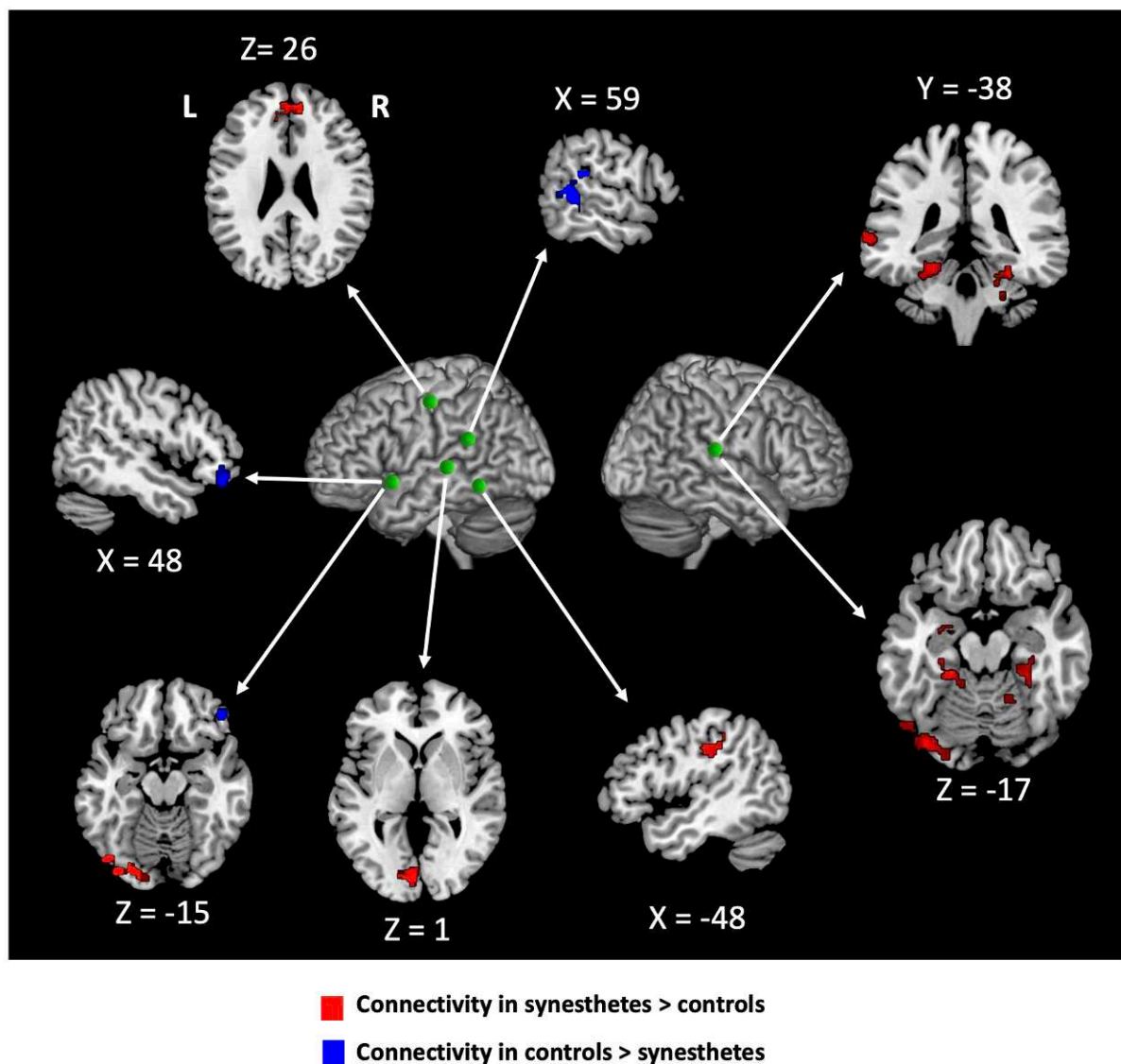


Figure 5.7

Experiment 3. Resting state connectivity. Regions with stronger (red) or weaker (blue) connectivity to the TTS network in synesthetes than in controls. Green spheres represent the centers of the TTS-network regions of interest showing group differences in connectivity.

5. Discussion

A. Summary and general parsing of the findings

A group of 17 tickertape synesthetes and matched controls were scanned while listening to speech (Experiment 1), viewing written words and other images (Experiment 2), and at rest (Experiment 3).

Across various analyses, synesthetes differed from controls by showing as a rule more intense activation and stronger functional connectivity. Those differences however may not all be specifically related to TTS. Indeed, in agreement with previous studies (Ward and Simner, 2022), a majority of the participants showed one or several other synesthesias associated with TTS (Hauw et al., 2023a). Some of the differences we found may be related to nonspecific brain predispositions eventually promoting distinct types of synesthesia (Ward and Simner, 2020).

On this background, our findings may be divided in two main ensembles. On the one hand, validating our first prediction, the contrast of activation during speech perception and during baseline showed over-activation in synesthetes in a set of left perisylvian and VOT regions (the TTS network), a direct correlate of the TTS phenomenon. In agreement with our second prediction, this increased activation concerned equally real and pseudo-words. Validating our third prediction, we observed a precise overlap of the TTS network with regions activated during reading and with regions involved in dyslexia, and the overlap of speech-related and reading-related areas was larger in synesthetes than in controls, demonstrating the predicted link between the two domains. On the other hand, we assessed functional connectivity during rest in Experiment 3, while TTS was not present. In agreement with our fourth prediction, we found over-connectivity in synesthetes between frontal and occipital regions distinct from the TTS network. This pattern may reflect predispositions to synesthesia which are not specific to TTS. Finally, analyses such as PPI provided some indications on how those two sets of findings may be coupled.

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The discussion will follow this general parsing of the results, followed by more general considerations.

B. Charting the TTS network

TTS requires the accurate mapping of input phonology to orthography, eventually allowing for the vivid conscious access to the resulting written pattern. We propose that this process is implemented by the TTS network, which largely overlaps with the reading system. We will consider in turn the main components of the TTS network, their involvement in the processing of speech and reading, and discuss their contribution to TTS.

Translating sounds into letters. The TTS network includes both anterior and posterior STG regions, with main peaks at MNI Y=-28 and Y=12, respectively (Figure 5.4). The STG is a complex mosaic deriving distinct representations from speech input, sometimes dissected in an anterior “what” and a posterior “how” pathway (Scott, 2019; Yi et al., 2019), respectively feeding lexical and non-lexical speech processing. Those two routes both contribute to TTS generation: indeed, univariate and multivariate differences between words and pseudowords did not differ between synesthetes and controls.

The lexical route to TTS. On the one hand, whenever synesthetes listen to words with an irregular orthography, they generally see them in their mind’s eye written according to their stored spelling (Hauw et al., 2023a). The anterior STG is thought to provide the input to word recognition (Binder, 2015; Bormann and Weiller, 2012; DeWitt and Rauschecker, 2012; Kohn and Friedman, 1986), and should therefore feed the lexical component of TTS. The posterior MTG, which we found both as part of the TTS network and when decoding words from pseudowords, may be the next step in lexical TTS generation (Supplementary figure 5.2). This region is activated during lexico-semantic tasks (Binder et al., 2009; Jedidi et al., 2021) and focal lesions yield lexical deficits (Boatman, 2000; Harvey and Schnur, 2015). The lexical involvement of the MTG also applies to reading, as it is consistently activated by words relative to pseudowords (for meta-analyses see McNorgan et al., 2015; J. S. Taylor et al., 2013). Thus the over-activated anterior STG and posterior MTG may support the lexical component of TTS, possibly in association with other lexical nodes showing no difference between groups such as the angular gyrus (Supplementary figure 5.1) (Binder et al., 2009).

The non-lexical route to TTS. On the other hand, when synesthetes are hearing pseudowords, they see them spelled-out in conformity with statistical correspondences between sounds and letters (Hauw et al., 2023a). The posterior STG, in association with the contiguous SMG, supports phonological representations for interfacing with other modalities, such as mapping to motor programs during speech repetition (Hickok and Poeppel, 2015), lip-reading (e.g. Dick et al., 2010; Hocking and Price, 2008; Wright, 2003), or reading and writing. There is ample evidence that the SMG is critical for computing phoneme-grapheme correspondences. Meta-analyses show that the SMG, where we could decode words from pseudowords (Supplementary figure 5.2), is often more activated by pseudowords than words (J. S. Taylor et al., 2013), and per-operative or transcranial stimulation of the SMG interferes specifically with phonological but not with lexical reading (Pattamadilok et al., 2010; Roux et al., 2012; Simos et al., 2000; M. W. Sliwinska et al., 2015). The posterior STG and the SMG may thus subtend the non-lexical component of TTS (Supplementary figure 5.2, bottom panel).

A premotor contribution to TTS? Finally, the left precentral component of the TTS network is commonly activated during speech production and perception (C. J. Price, 2012), but also during reading, with stronger activation for naming than lexical decision, for pseudowords than for words, and for longer than shorter stimuli (F. Bouhali et al., 2019; J. S. Taylor et al., 2013). It is thought to support covert speech planning, in close interaction with speech perception (Wilson et al., 2004). One may therefore suppose that, although over-activated in synesthetes, the premotor cortex had no causal contribution to TTS.

Orthography and the VWFA. A further component of the TTS network was the VWFA, as evidence by its perfect overlap with reading-induced activation. The VWFA is best known as the entry gate for written words into the brain, but there is converging evidence that it also contributes to orthographic mental imagery, an ability possessed to some level by all literate individuals (Bourlon et al., 2009; Holm et al., 2015). Thus, brain-damaged alexic patients may lose orthographic imagery following damage to the VWFA (Bartolomeo et al., 2002; Rosazza et al., 2007; Sirigu and Duhamel, 2001; Volpato et al., 2012). In healthy individuals, the VWFA is activated not only by strings of letters, but also during speech perception (see Figure 5.1, Cohen et al., 2021; Ludersdorfer et al., 2016; Yoncheva et al., 2010)), suggesting that such top-down influences from the lexical and non-lexical routes are the source of orthographic

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imagery. The over-activation of the VWFA which we observed in synesthetes would be the correlate of their exceptionally vivid and automatic imagery.

We could delineate the TTS network by using activation paradigms focused at the specific type of synesthesia we are studying. However, a majority of participants had at least one other associated synesthesia. Using resting state data, collected while TTS was not occurring, we tried to find more general predispositions to synesthesia, not necessarily specific to TTS.

C. Fronto-occipital resting-state connectivity

During rest, the left IFS and pre-SMA had stronger Global Correlation in synesthetes than in controls, specifically with the bilateral occipital cortex. The role of the prefrontal-occipital duo in controlling visual consciousness has been demonstrated in a variety of settings. According to the global neuronal workspace theory, the access of perceptual representations to consciousness results from re-entrant sharing of information between sensory regions and a supramodal network with critical prefrontal nodes (Dehaene and Changeux, 2011). Thus the perception threshold for masked visual stimuli is raised in patients with focal left prefrontal lesions (Del Cul et al., 2009), in multiple sclerosis patients with lesions to the prefrontal white matter and specifically to the fronto-occipital fasciculus (Reuter et al., 2009), and in schizophrenic patients with lower anisotropy in this same fasciculus (Berkovitch et al., 2021). In neglect patients, prefrontal and occipital regions are more activated whenever stimuli presented on the neglected side are perceived than when they are omitted (Rees et al., 2002). In healthy individuals, prefrontal activation is stronger when deficient masking allows for better subjective report of stimuli, at the exact location of our IFS cluster (Lau and Passingham, 2006). Finally, prefrontal and occipital activation appears reproducibly in a meta-analysis of studies comparing activations between physically identical conscious vs unconscious stimuli (Bisenius et al., 2015).

The same regions may control not only the perception of external stimuli, but also the perception of internally generated mental images (for a review see Dijkstra et al., 2019). The activation of the dorsolateral and pre-SMA prefrontal cortex is modulated both by stimulus visibility during perception and by vividness during mental imagery (Dijkstra and Fleming, 2023). Moreover, closer to our finding of increased fronto-occipital correlation in synesthetes, the functional connectivity between prefrontal and occipital areas contributes to mental

imagery. Thus dynamic causal modelling reveals stronger excitatory influence from prefrontal to occipital cortex during imagery than during perception (Dijkstra et al., 2017). Individuals with particularly vivid mental images (hyperphantasia) show stronger fronto-occipital connectivity during rest as compared to participants unable to generate mental images (aphantasia, Milton et al., 2021). In this context, the increase in fronto-occipital connectivity which we found in synesthetes could contribute to TTS by raising to consciousness orthographic representations which usually remain subliminal (Chéreau et al., 2007; Pattamadilok et al., 2010; Ziegler et al., 2008). However, those regions play no specific role in reading, and this hyper connectivity may be expected to favor other types of synesthesia, at least those with a visual content, consistent with our observation that most of our participants had other associated synesthesias (Hauw et al., 2023a).

D. Predisposition for TTS or dyslexia

What is the contribution to TTS of the two differences which we observed between synesthetes and controls, namely the TTS network over-activation and the fronto-occipital over-connection? Ward (2019) proposed that any given synesthesia results from the combination of a general “synesthetic disposition”, plus innate or acquired factors steering the brain toward specific phenotypes. The general disposition surfaces, among other features, as a moderate but consistent superiority of synesthetes in mental imagery vividness (K. Barnett and Newell, 2008; Price, 2009; Spiller et al., 2015), and in subjective sensory sensitivity – for instance to aversive visual glare – (Van Leeuwen et al., 2019; Ward et al., 2017). Across subjects, stronger synesthetic disposition would result in a higher number of associated synesthesias, a parameter which is itself correlated with several scales of imagery vividness (Spiller et al., 2015). We assessed this hypothesis by computing the correlation across synesthetes between the number of associated synesthesias and the average Global Correlation value in the left IFS which we identified based on its higher Global Correlation in synesthetes than in controls (Supplementary figure 5.5). We found that participants with a broader set of synesthesias tended to have higher Global Correlation, which should encourage further exploration. As discussed before, prefrontal regions and their connections to the occipital cortex, considering their involvement in perception and imagery, likely contribute to the synesthetic disposition. In this framework, the TTS network would instantiate the functional mechanisms specific to TTS, as opposed to other synesthesias.

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The emergence of TTS results from the association of two factors: innate peculiarities in the early make-up of left-predominant areas or connections, “neuronal recycling” of those systems for reading acquisition (Stanislas Dehaene and Cohen, 2007). The association of cerebral biases with the learning of reading generally results in dyslexia rather than in TTS, but we showed that common brain systems are affected in both cases (Figures 5.2, 5.4, 5.5). To a point, TTS and dyslexia have opposite cerebral signatures. Considering univariate activation, the ROIs depicted in Figure 5.2 are activated below the normal level in dyslexia during reading, and above the normal level in TTS during speech perception. This pattern supports the idea that peculiarities of the reading system reduce its bottom-up activation from sight in dyslexia, and increase its top-down activation from speech in TTS. Disregarding the variety of dyslexias, this view would exclude the association of dyslexia with TTS, a negative prediction which remains to be assessed.

Atypical activation may be associated with atypical functional connectivity among regions of the reading network. In the case of TTS, we found increased connectivity between left temporo-parietal areas and the VWFA, with both PPI analyses (Figure 5.3) and resting state connectivity (Figure 5.7). In stark contrast, ever since Horwitz et al.’s (1998) study, reduced connectivity has been found repeatedly in dyslexic individuals, mostly between the VWFA and the IPL and/or the lateral prefrontal cortex. This pattern prevails in adults (Schurz et al., 2015), children (Di Pietro et al., 2023; van der Mark et al., 2011; Zhou et al., 2015), but also in 4-13 month-old infants, in whom the only predictor of family risk of dyslexia was weaker resting state connectivity of the VWFA, first and foremost with the left IPL and prefrontal frontal regions (Yu et al., 2022). The latter result provides a unique view in the cerebral predisposition for dyslexia long before reading acquisition; one may speculate that specific predispositions for TTS should involve some form of over-connectivity among the same regions.

We proposed that TTS results from the interaction of two components: a fronto-occipital system facilitating conscious access, and an atypical reading system. However it is unclear how those two components interact to generate TTS. One may note that during rest, synesthetes showed increased cross-connectivity between both components (Figure 5.7): the precentral ROI was over-connected to the pre-SMA, and both superior temporal ROIs to the occipital cortex. Such regions of overlap may contribute to the vivid imagery of the orthographic

content elicited in the reading system due to increased top-down influence from speech areas to the VWFA.

The current results are consistent with a previous single-case study of a TTS synesthete, who also participated in the current study, with entirely independent data (Hauw et al., 2023c). During speech perception, MK showed over-activation of the core components of the TTS network, i.e. the left SMG, VWFA, and precentral cortex. The present group study extended this set of regions to the lateral temporal cortex, and did not replicate the mesial frontal and parietal activations observed in MK. The group study also confirms and generalizes the overlap of the TTS network with regions supporting word reading.

E. Limitations and future directions

The subjective nature of TTS makes it difficult to define rigorous inclusion criteria, as those rely only on the participants' self-report. We developed extensive questionnaires for exploring individually the subjective features of TTS and checking their consistency (Hauw et al., 2023a). We also showed that TTS synesthetes perform measurably better than typical subjects in tasks requiring visual orthographic imagery, such as backward spelling or letter counting with auditory words (Hauw et al., 2023b). Such tools will allow us to derive more objective and quantitative criteria of TTS, following the example of grapheme-color synesthesia (Carmichael et al., 2015; Eagleman et al., 2007).

Moreover, there is individual variability in the synesthetic experience (location, color, vividness, etc). The underlying functional variability could not be elucidated in this study. For instance, only two participants could be considered as “projectors” on the basis of their introspection. Exploratory comparison of those two individuals with the other (“associator”) synesthetes revealed no differences. Clarifying those delicate issues would require larger samples of participants, and possibly time-resolved imaging techniques (Michalareas et al., 2023).

Our results put to light key functional features of TTS, but provide no evidence on potential anatomical abnormalities, which may clarify the developmental causes of TTS and discriminate among general theories of synesthesia (Grossenbacher and Lovelace, 2001; Hubbard and Ramachandran, 2005). Is the over-connectivity which we identified in synesthetes subtended by atypical anatomical connections? Do regions with an increased

Subtitled speech: the neural mechanisms of tickertape synesthesia

Discussion

activity also show atypical anatomical features? Answering those questions will require the use of diffusion imaging and of morphometric techniques. A different take on the issue of causality would consist in using TMS (Murakami et al., 2013; Valero-Cabré et al., 2017) to zap components of the TTS network and study interferences with TTS, as was done with other types of synesthesia (Esterman et al., 2006; Terhune et al., 2011).

We proposed that TTS results from strong top-down activation from phonological to orthographic regions, specifically from the SMG to the VWFA. This hypothesis is consistent with the fMRI data, but actually observing the information flow and the time-course of phonological and orthographic codes would require time-resolved techniques (EEG/MEG), which have been successfully applied to grapheme-color synesthesia (e.g. Brang et al., 2010; Teichmann et al., 2021).

Finally, longitudinal studies in children, prior to, during and after reading acquisition would be crucial for identifying synesthetic predisposition, observing the emergence of activation patterns associated with synesthesias involving orthography, and their relationships with typical reading-related activations (Dehaene-Lambertz et al., 2018; Simner et al., 2009), evaluating the early incidence of TTS and its stability over time, and the relationships between TTS and dyslexia. Such studies could be practically set up as ancillary components of broader studies of reading development.

Subtitled speech: the neural mechanisms of tickertape synesthesia

We have found an increase in connectivity in synesthetes compared with controls, on functional MRI or when listening to speech. Another way of studying these differences in connectivity, is to analyse the brain's overall network organization, using graph-theoretical analyses. In collaboration with Juliana Gonzalez-Astudillo and Fabrizio De Vico Fallani, we studied the differences between our two groups of participants using these analyses.

Increased core-periphery connectivity in tickertape synesthetes.

CHAPTER VI

**Increased core-periphery connectivity in
tickertape synesthetes.**



Increased core-periphery connectivity in ticker-tape synesthetes

 Fabien Hauw,^{1,2†}  Juliana Gonzalez-Astudillo,^{3,†}  Fabrizio De Vico Fallani³
and Laurent Cohen^{1,2}

[†]These authors contributed equally to this work.

1 Inserm U 1127, CNRS UMR 7225, Sorbonne Universités, Institut du Cerveau, ICM, Paris 75013, France

2 AP-HP, Hôpital de La Pitié Salpêtrière, Fédération de Neurologie, Paris 75013, France

3 Sorbonne Université, Paris Brain Institute—ICM, CNRS, Inria, Inserm, AP-HP, Hôpital de la Pitié Salpêtrière, Paris F-75013, France

Correspondence to: Fabien Hauw
PICNIC-Lab, Hôpital Pitié, 47 Bd de l'Hôpital, 75013 Paris, France
E-mail: fabien.hauw@orange.fr

We read with great interest the article by Sokolowski and Levine,¹ proposing that distinct neurodevelopmental disorders share common pathophysiological mechanisms, only discernible when considering the brain's overall network organization.² Sokolowski and Levine¹ propose that those disorders share reduced anatomical and functional connectivity between the 'core' and the 'periphery' of brain networks, especially preventing some perceptual contents to access conscious awareness. The core-periphery structure is key for the overall integration of information and derives from graph-theoretical approaches to large-scale brain organization, in which regions and their connections are modeled as the nodes and the links of complex networks. Informally, the dense 'core' is a subgroup of tightly connected nodes, while the 'periphery' consists of sparse nodes, which are preferentially connected to the core and loosely connected among them.³ The view of Sokolowski and Levine¹ is chiefly supported by evidence of impaired connectivity in dyslexia and related disorders. However, evidence is much scarser for backing the symmetrical and critical prediction that increased core-periphery connectivity should yield atypical abilities, such as enhanced awareness of some cognitive contents.

Some persons perceive vividly and automatically in their mind's eye the written form of words that they are hearing, a developmental peculiarity known as 'ticker-tape synesthesia' (TTS).^{4–6} Here we propose to view TTS as the opposite of dyslexia in terms of brain connectivity. Assuming that, in dyslexia, reduced access from orthography to words' sounds and meaning is grounded in reduced core-periphery connectivity, then our prediction is that in TTS, increased access to orthography from speech should be associated with increased core-periphery connectivity.

To test this prediction and assess a logical consequence of the theory proposed by Sokolowski and Levine,¹ we collected functional MRI resting-state data in a group of 17 right-handed TTS synesthetes and in 17 matched control participants. We performed individual graph-theoretical analyses, with special emphasis on the core-periphery relationships, and compared synesthetes with controls (see details in the [Supplementary material](#)).

The cortex was parcellated into 246 symmetrical regions (or nodes), and for each participant we computed the pairwise Pearson's correlation between the time series of the nodes. The individual correlation matrices corresponding to weighted connectivity networks served as the input to all subsequent analyses.

We first considered the node's strength, measuring the sum of all the weighted connections that a node has with the rest of the network ([Supplementary Fig. 1](#)). Sixteen nodes had higher strength in synesthetes than in controls ($P < 0.05$ uncorrected), 11 in the left and 5 in the right hemisphere ([Fig. 1A](#) and [Supplementary Table 1](#)). No node had higher strength in controls. As only strongly connected nodes are candidate members of the core, those 16 nodes were then selected for subsequent analysis of coreness.

We computed each node's coreness, a probabilistic measure ranging from 0 to 1 indicating the tendency of a node to be part of the core rather than the periphery ([Supplementary Figs 2 and 3](#)).⁷ To ensure the reliability of our analysis, coreness was further normalized by equivalent randomized networks preserving the node strength distribution, thereby removing bias due to possibly existing interindividual differences in the total strength. Our analysis revealed five nodes with significantly higher coreness in synesthetes compared to controls [$P < 0.05$, false discovery rate (FDR) corrected], including three in the left hemisphere and two in the right hemisphere ([Fig. 1B](#) and [Supplementary Table 1](#)). These nodes were located in bilateral prefrontal and left parietal regions. Interestingly, in the control group, all five nodes tended to belong to the periphery, as indicated by their lower coreness values. In contrast, in synesthetes four of these five nodes tended to be positioned within the core, as reflected by their higher coreness ([Fig. 1C and D](#)).

These results suggest a transition of these five nodes from the periphery to the core of the network in the synesthetic individuals that is likely due to a preference to establish stronger connections with the core regions and not with the peripheral ones. We assessed this prediction in two steps. First, we computed the group-averaged connectivity of each node with these five highlighted nodes and

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Hauw F. ^{a,b*}, Gonzalez-Astudillo J. ^{a*}, de Vico Fallani F. ^a, Cohen L. ^{a,b}

a. Inserm U 1127, CNRS UMR 7225, Sorbonne Universités, Institut du Cerveau, ICM, Paris, France

b. AP-HP, Hôpital de La Pitié Salpêtrière, Fédération de Neurologie, Paris, France

* These two authors contributed equally to this work.

1. Introduction

We read with great interest the article by Sokolowski and Levine (2023), proposing that distinct neurodevelopmental disorders share common pathophysiological mechanisms, only discernible when considering the brain's overall network organization (Van Den Heuvel and Sporns, 2019). Sokolowski and Levine propose that those disorders share reduced anatomical and functional connectivity between the “core” and the “periphery” of brain networks, especially preventing some perceptual contents to access conscious awareness. The core-periphery distinction derives from the graph-theoretical approach to large-scale brain organization, in which regions and their connections are theorized as the nodes and the edges of complex graphs. Informally, the dense “core” is a hub of tightly connected nodes, while the “periphery” consists of sparse nodes, which are preferentially connected to the core and loosely connected among them (Bassett et al., 2018). Sokolowski and Levine's view is chiefly supported by evidence of impaired connectivity in dyslexia and related disorders. However, evidence is much scunter for backing the symmetrical and critical prediction that *increased*

core-periphery connectivity should yield atypical abilities, such as enhanced awareness of some cognitive contents.

Some persons perceive vividly and automatically in their mind's eye the written form of words that they are hearing, a developmental peculiarity known as "ticker-tape synesthesia" (TTS) (Galton, 1883; Hauw et al., 2023a, 2023c). We propose that TTS may be the opposite of dyslexia in terms of brain connectivity, and adduce key evidence to the theory proposed by Sokolowski and Levine (2023). In dyslexia, reduced access from orthography to words' sounds and meaning may be grounded in reduced core-periphery connectivity. Our prediction was that conversely, in TTS, increased access to orthography from speech should correspond to increased core-periphery connectivity.

In order to test this prediction, we collected fMRI resting-state data in a group of 17 right-handed TTS synesthetes and in 17 matched control participants, and we performed graph-theoretical analyses, with special emphasis on the core-periphery relationships.

2. Methods

A. Participants

We created a short description of TTS, and recruited participants by broadcasting it through email and social networks, targeting particularly groups of students and university members, and groups devoted to synesthesia, psychology, and neuroscience. We thus recruited 22 tickertape synesthetes, plus 22 controls matched one-to-one to synesthetes based on age, gender, education level and handedness. We excluded 5 left-handed participants in each group, resulting in 2 groups of 17 participants. All participants were native French speakers, right-handed according to the Edinburgh Inventory (Oldfield, 1971), had normal or corrected-to-normal vision and hearing, and had no history of neurological or psychiatric disorders. They were a subset of the participants in a behavioral study of TTS (Hauw et al., 2023b). The research was approved by the institutional review board of the INSERM (protocol C13-41), and all participants provided informed written consent in accordance with the Declaration of Helsinki.

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B. MRI acquisition and preprocessing

All images were acquired on a Siemens 3T MAGNETOM Prisma scanner. T1-weighted anatomical images (TR/TE/flip angle = 2400 ms / 2.23 ms / 9°, voxel size = 0.7 × 0.7 × 0.7 mm) were acquired with a 64-channel receive-only head coil. For functional images, we used multi-echo fMRI sequences (Posse, 2012): time repetition (TR) = 1660 ms; multi-time echo (TE) = 14.2, 35.39, 56.58 ms; flip angle = 74°; voxel size = 2.5 × 2.5 × 2.5 mm; 60 slices; 20-channel receive-only head coil. Cardiac and breathing frequencies were recorded using a pneumatic breathing belt and a pulse oximetry unit.

Using CAT12 (<http://www.neuro.uni-jena.de/cat>), anatomical volumes were segmented, normalized to the standard MNI stereotactic space and resampled to 1.5 × 1.5 × 1.5 mm. Functional images were processed as follows. Using `afni_proc.py`, all echoes time-series were despiked and slice-time corrected. Motion correction was computed on the first echo with the volume with the lowest motion as reference, then applied to all echoes, and finally merged using optimal combination `t2smmap.py` (see `meica.py` provided with AFNI: <http://afni.nimh.nih.gov/afni/>). Finally, using SPM12 (Wellcome Institute of Imaging Neuroscience, London, UK) implemented in Matlab, functional time-series were co-registered to the anatomical volume, then normalized to Montreal Neurological Institute (MNI)-space (2.5mm isotropic), and spatially smoothed (5mm full-width at half-maximum [FWHM] isotropic).

C. Procedure

For 10 minutes, participants had to fixate a central white cross on a black screen, while the room was in darkness.

D. Preprocessing

Images were first processed through the same general pipeline as Experiments 1 and 2. Then, applying the default settings of the Functional Connectivity Toolbox (CONN) (Whitfield-Gabrieli and Nieto-Castanon, 2012), the signal from the white matter and CSF was regressed out, and a linear detrending and a band-pass filter of 0.008–0.09 Hz were applied.

E. Graph-theoretical analyses

Using CONN, functional images were parcellated into 246 regions, 123 for each hemisphere, derived from the Brainnetome atlas (Fan et al., 2016). Then we computed the “ROI to ROI” connectivity, which is the computation of the correlation between each region and the others. For each region, its auto-correlation value was set to 0, and only positive values were kept for graph theoretical analyses.

Considering a network of N nodes, we then compute the **strength** s_i of each node i ($i = 1, \dots, N$), which corresponds to the sum of the connection weights that each node i establishes with the rest of the network,

$$s_i = \sum_{i \neq j}^N w_{ij} \quad (1)$$

From now on, we refer to s_i as the *richness* of node i . Notice that this is the simplest way to define the *richness* of a node, and different metrics such as other measures of node centrality, can be as well used. Then we divide the links of a node i in two groups, those towards nodes with lower *richness* (s_i^-) and those towards nodes with higher *richness* (s_i^+). Hence, we can specifically decompose the strength of node i as

$$s_i = s_i^- + s_i^+. \quad (2)$$

This metric evaluates the importance of a node by highlighting the magnitude of its connections, yet it fails capturing the node’s structural role within the network.

The brain works as a functional hierarchical organization, where a subset of network elements act as a critical backbone or information processing core – a densely connected and topologically central subgraph. To assess this structure, we applied the concept of core-periphery, identifying core nodes characterized by their propensity to form denser connections among themselves than with other brain regions, from where they receive integrative information, while the remaining lower strength nodes form the periphery. To quantify this structural organization, we estimate the node coreness (C_i), the normalized number of thresholds at which the corresponding node is present in the rich core (Battiston et al., 2018; Ma and Mondragón, 2015).

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Methods

Then the nodes of the network are ranked according to their *richness* s , so that the node i with the best rank, i.e., rank=1, is the node with the largest value of s , the node rank=2 is the one with the second largest value of s , and so on. We then compute for each node i the value of s_i^+ as a function of rank i . The value of the rank corresponding to the maximum of s_i^+ finally determines the core-periphery structure. All nodes with rank lower than such a value are assigned to the core, whereas the remaining ones become part of the periphery.

We repeat this procedure across an increasing full range of density thresholds ($\delta_n = n/(N - 1)$ with $n = 1, \dots, N-1$). At each threshold, we adjust the weighted network by preserving a proportion equivalent to δ_n of the strongest weights, with the last thresholds resulting in a fully connected network. This results in a core-periphery matrix of zeros and ones (0: periphery, 1: core) with size $N \times N - 1$, where the row entries correspond to each of the nodes and the columns to the density thresholds. Finally, we obtained the Coreness value by averaging each node across all the thresholds.

Graph statistical analysis

Given that the criteria for defining richness within the coreness (C) formulation can be associated with robust connections —such as in the case of high strength nodes— we conducted the statistical analysis on the normalized coreness coefficient. We normalized the coreness value obtained from the actual network by comparing it with the average derived from a collection of 100 randomized networks ($C/\langle C_{rand} \rangle$). To ensure the comparability of the randomized networks, they were generated from the original graph by randomly reshuffling the edges while maintaining the distribution of the original node strength (Bertolero et al., 2017; Maslov and Sneppen, 2002; Rubinov and Sporns, 2010).

Considering the substantial disparity between the number of nodes (246) and subjects (17 per group), the application of a p-value correction introduces a substantial penalization, rendering the attainment of significant corrected p-values challenging. To overcome this issue, we focused our attention on a specific subgroup of nodes that exhibit a significant difference between synesthetic and control subjects in terms of strength (16 nodes with $P < 0.05$ not corrected, see Figure 6.1A). Subsequently, we conducted a statistical analysis of coreness within this subgroup. Importantly, the coreness False Discovery Rate (FDR) correction was exclusively applied to this subgroup.

3. Results

The cortex was divided into 246 symmetrical regions (or nodes), and for each participant we computed the pairwise correlation of time series between nodes. The individual correlation matrices served as the input to all subsequent analyses.

We first computed each node's Strength, a measure of its average connectivity with all other nodes. Sixteen nodes had higher Strength in synesthetes than in controls ($P < 0.05$ uncorrected), 11 in the left and 5 in the right hemisphere (Figure 6.1A and Table 6.1). No node had higher Strength in controls. As only strongly connected nodes are candidate members of the core, those 16 nodes were selected for subsequent analysis of Coreness.

Table 6.1

Ref	Node name	side	<i>S</i> t-val	<i>S</i> p-val	<i>C</i> _{syn}	<i>C</i> _{ctr}	<i>C</i> t-val	<i>C</i> p-val (FDR)
1	medial area 9	left	3.00	5.15e-03	0.76	0.32	4.13	3.85e-03**
2	caudal area 40(PFm)	left	2.69	1.13e-02	0.77	0.38	3.64	7.51e-03**
3	medial area 9	right	2.60	1.39e-02	0.78	0.39	3.35	1.12e-02*
4	ventral area 9/46	right	2.35	2.52e-02	0.76	0.48	3.11	1.58e-02*
5	area 46	left	3.45	1.58e-03	0.53	0.14	2.81	2.65e-02*
6	lateral area 5	left	2.90	6.71e-03	0.55	0.26	2.58	3.39e-02*
7	rostradorsal area 39(Hip3)	left	2.07	4.62e-02	0.58	0.21	2.51	3.45e-02*
8	lateral area 12/47	left	2.63	1.31e-02	0.83	0.54	2.63	3.50e-02*
9	ventral area 9/46	left	2.32	2.70e-02	0.60	0.30	2.30	4.96e-02*
10	caudal area 40(PFm)	right	2.72	1.04e-02	0.85	0.63	2.16	6.19e-02

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11	anterior superior temporal sulcus	left	2.35	2.53e-02	0.74	0.50	1.67	1.53e-01
12	medial area 8	left	2.10	4.41e-02	0.48	0.27	1.39	2.33e-01
13	caudal area 21	left	2.51	1.74e-02	0.69	0.47	1.21	2.91e-01
14	rostral area 45	left	2.25	3.16e-02	0.62	0.50	1.11	3.13e-01
15	ventrolateral area 8	right	2.54	1.60e-02	0.69	0.47	0.70	4.87e-01
16	dorsal area 23	right	2.51	1.74e-02	0.76	0.64	0.71	5.14e-01

Table 6.1. Nodes with a higher strength in synesthetes than in controls

List of nodes with a higher strength in synesthetes than in controls. Columns S t-val and S p-val are for t-value and p-value of each node respectively, resulting of the T-test between synesthetes and controls for the Strength. No correction for multiple comparisons is applied on Strength p-values. Columns C syn and C ctr are the coreness value of each node for the synesthetes and controls respectively. Columns C t-val and C p-val are the same metrics as S t-val and S p-val but resulting of the T-test between synesthetes and controls for the Coreness, and C p-val are FDR-corrected p-values. Only nodes on the 9 first entries have a significant higher Coreness in synesthetes than in controls.

* $P < 0.05$, ** $P < 0.01$

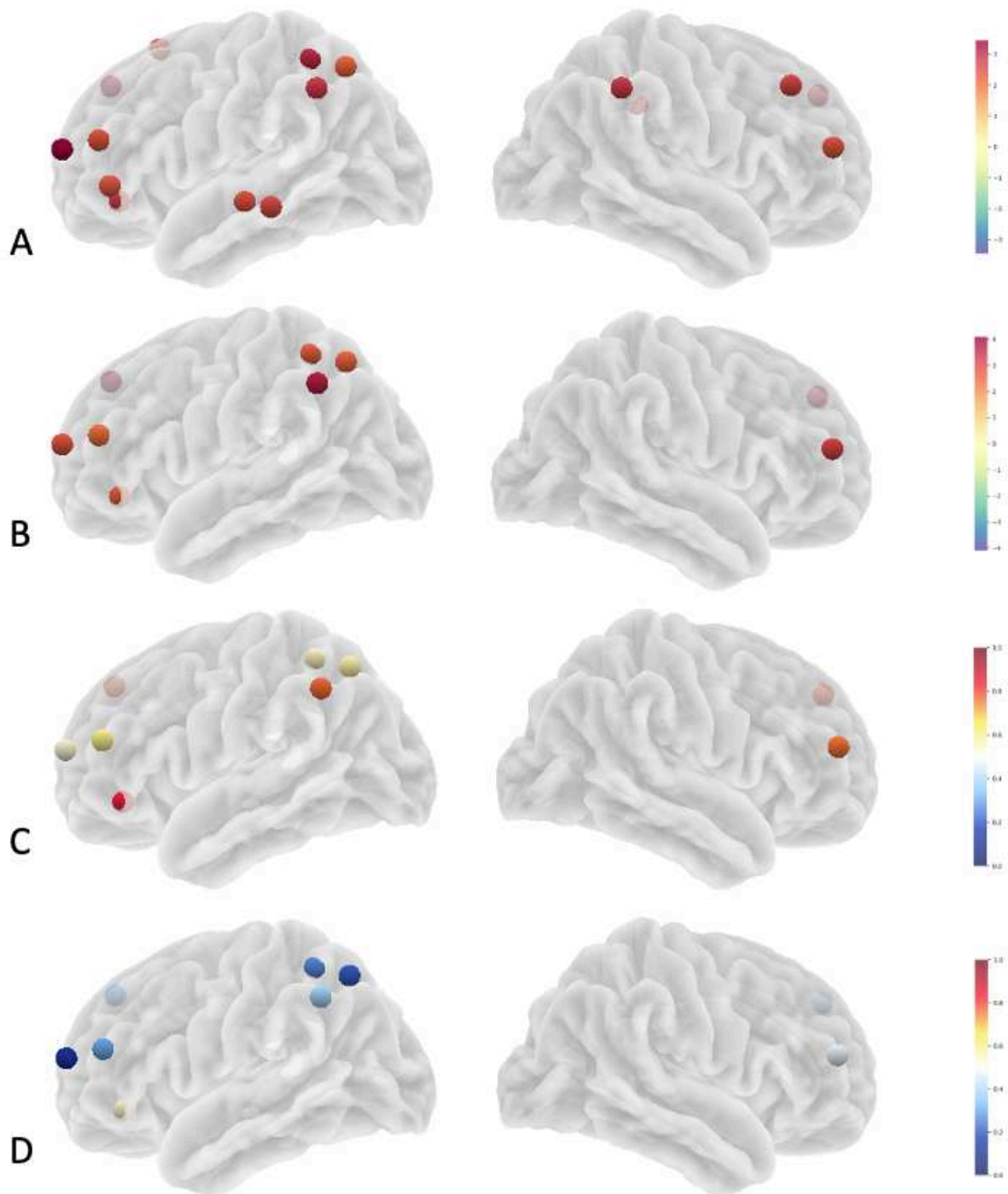
Coreness is a measure in the 0-1 range of each node's tendency to belong to the core rather than to the periphery. Coreness was normalized by randomizing the network while preserving strength distribution, such that Coreness was independent from Strength. We found that 9 nodes had higher Coreness in synesthetes than in controls ($P < 0.05$, FDR corrected), 7 in the left hemisphere and 2 in the right hemisphere (Figure 6.1B and Table 6.1). The nodes with an increased coreness in synesthetes were located in bilateral frontal and left parietal regions. This result also emphasizes the notion that nodes exhibiting significant strength differences do not necessarily manifest significant differences in terms of coreness. Conversely, no node had higher Coreness in controls.

Increased core-periphery connectivity in tickertape synesthetes.

Results

In controls, 8 out of those 9 nodes had a Coreness closer to 0, that is tended to belong to the periphery. In contrast, in synesthetes all 9 nodes had a Coreness closer to 1, that is now tended to belong to the core (Figure 6.1C-D).

Figure 6.1



Increased core-periphery connectivity in tickertape synesthetes.

Results



Figure 6.1. (A) In 16 nodes, Strength was significantly higher in synesthetes than in controls ($p < 0.05$), without correction for multiple comparisons. (B) In 9 out of these 16 nodes, synesthetes had a higher Coreness than controls ($p < 0.05$ FDR). In both (A) and (B) panels, nodes with a higher Strength and/or Coreness in synesthetes than controls tend to be in red. (C) In all those 9 nodes, Coreness was ≥ 0.5 in synesthetes, while in controls (D), it was ≤ 0.5 in 8/9 nodes in controls. (E) Each number corresponds to the entries in Table 6.1.

Finally, we determined what were on average the preferential connection partners of the 9 nodes with increased Coreness (Figure 6.2A). Their Strength of connectivity was higher in synesthetes than in controls mainly with bilateral frontal regions, but also parietal and to a lesser extent, temporo-occipital regions. Given that increased Coreness implies that a given node is more connected to other Core nodes rather than to periphery nodes, we wanted to investigate the relationship between 1/ the Strength of connectivity of each node with the others, and 2/ the Coreness of these nodes. In synesthetes, there was a positive correlation between how each of these 9 nodes connect with another one, and the Coreness of this connection partner. In controls, such a positive correlation is less visible (Figure 6.2B). Except for the 6th and 7th nodes, the high correlation is remarkably consistent across the nodes and participants.

Figure 6.2

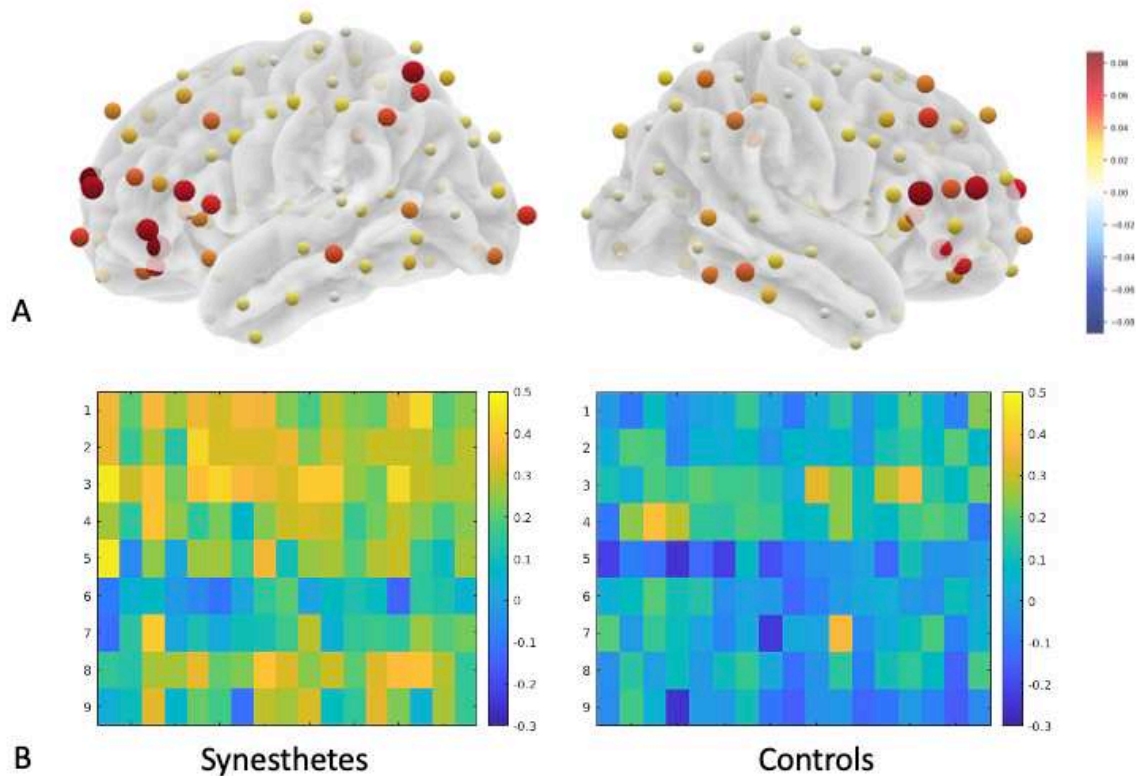


Figure 6.2. (A) In each group separately, we computed the mean signal correlation of the 9 nodes with a higher Coreness in synesthetes, with every other node from the atlas. We then computed the difference between both groups. We found a higher correlation of these nodes mainly with the fronto-parietal regions, but also with left STS and occipital nodes. (B) Correlation of 1/ the Strength of each node of the 9 nodes with increased Coreness, with other nodes with 2/ the Coreness of these nodes. Lines represent the nodes, numbered in the same order as in the Table 6.1. Columns represent the participants. Left panel is the correlation for synesthetes, right panel is for controls.

4. Discussion

In summary, we showed that a set of mostly left-hemispheric brain regions have increased Coreness in synesthetes as compared to controls. In other words those regions, which in controls tend to belong to the periphery of the brain graph, show increased connectivity with the brain core in synesthetes. Although the exact same analyses have not been performed in dyslexia, the graph patterns may be seen as opposite in the two conditions. Thus connectivity is reproducibly reduced between left inferior parietal and prefrontal regions in dyslexics

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Discussion

(Schurz et al., 2015), contrasting with increased integration of those regions in synesthetes (Figure 6.1). This difference might in turn be related, in the two contrasting conditions, to reduced awareness of phonology (Boets et al., 2013) vs increased awareness of orthography (Hauw et al., 2023c), and to impaired vs enhanced (Hauw et al., 2023b) performance with written words.

In summary, TTS fills a critical gap by supporting the validity of Sokolowski and Levine's proposal on the consequences of atypical core-periphery relationships, in the field of reading abilities.

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Our functional connectivity results suggest a role for the connection between occipital cortex and left frontal cortex in synesthesia. We also studied this connection in a reverse situation of diminished perception, in a patient who, following a reversible posterior encephalopathy syndrome, developed cortical blindness. The particularity of this case was that the primary visual cortex was partially preserved, with lesions mainly in associative visual areas.

CHAPTER VII

Study of conscious access to visual perception in a patient with cortical blindness

Are we aware of neural activity in primary visual cortex?

A neuropsychological case-study.

Authors: Fabien Hauw ^{a,b}, Aude Sangaré ^{a,b}, Esteban Munoz ^a, Claire Meyniel ^c, Nina Di Donato ^d, Sylvie Chokron ^{d,e}, Frédérique Bozon-Auclair ^b, Lionel Naccache ^{a,b,c*}

a. Sorbonne Université, Institut du Cerveau - Paris Brain Institute - ICM, Inserm, CNRS, Paris, France- Sorbonne Université, UPMC Univ Paris 06, Faculté de Médecine Pitié-Salpêtrière, Paris, France

b. AP-HP, Hôpital Groupe hospitalier Pitié-Salpêtrière, DMU Neurosciences, Department of Neurology, Paris, France

c. AP-HP, Hôpital Groupe hospitalier Pitié-Salpêtrière, DMU Neurosciences, Department of Clinical Neurophysiology, Paris, France

d. Institut de Neuropsychologie, Neurovision, NeuroCognition, Fondation Ophtalmologique Rothschild, Paris 75019, France

e. Integrative Neuroscience and Cognition Center, UMR 8002, CNRS & Université de Paris, Paris 75006, France

1. Abstract

According to a seminal hypothesis stated by Crick and Koch in 1995 one is not aware of neural activity in primary visual cortex (V1) because this region lacks reciprocal connections with

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Introduction

prefrontal cortex (PFC). We provide here a neuropsychological illustration of this hypothesis in a patient with a very rare form of cortical blindness: ventral and dorsal cortical pathways were lesioned bilaterally while V1 areas were partially preserved. Visual stimuli escaped conscious perception but still activated V1 regions that were functionally disconnected from PFC. These results strengthen the causal role of PFC in visual awareness.

2. Introduction

In a seminal paper published more than a quarter century ago, Crick and Koch hypothesized that one is not aware of neural activity that occurs in primary visual cortex (V1) (Crick & Koch, 1995). They proposed that the lack of direct reciprocal neuronal connections between prefrontal cortex (PFC) and V1 (Felleman & Van Essen, 1991) should prevent awareness of V1 activity. We would only be aware of visual representations coded within ventral (occipito-temporal) or dorsal (occipito-parietal) cortical pathways, that are fed by V1 and connected to PFC (Ungerleider, 1982). This prediction is difficult to test in healthy volunteers in whom V1 is connected indirectly to PFC through ventral and dorsal cortical pathways. Checking its validity is still crucial today because it is compatible with only one group of current theories of consciousness (Ahissar & Hochstein, 2004; Dehaene & Naccache, 2001; Lau & Rosenthal, 2011), while incompatible with another group (Lamme, 2006; Tononi, 2012; Tononi et al., 2016). We provide here a case-report compatible with this prediction through the exploration of a neurological patient with cortical blindness caused by an extremely rare pattern of posterior brain lesions: while ventral and dorsal cortical pathways were severely lesioned in both hemispheres, V1 areas were partially preserved. Using a set of behavioral, electrophysiological and fMRI data, we show visual stimuli were still activating V1 areas in this patient, but that bilateral lesions of ventral and dorsal pathways abolished the indirect functional connectivity between V1 and PFC present in healthy sighted volunteers.

3. Methods, Results & Discussion

A 59 y.o. male patient free of any prior neurological or psychiatric history was hospitalized in Intensive Care Unit for an acute respiratory distress syndrome secondary to SARS-Cov2

Study of conscious access to visual perception in a patient with cortical blindness

Methods, Results & Discussion

infection. He presented several complications and notably a severe posterior encephalopathy syndrome with refractory status epilepticus. We examined and tested this patient between February-August 2021 (see Supplementary Material for Ethical agreement and consent, and for detailed clinical report), and his condition was stable across all sessions: when awake, he was conscious and aware of his blindness. He often complained about it (e.g.: *'I am so so sad, I am blind, I can't see!'*), with emotionally congruent facial and prosodic expressions of sadness. He also showed the following cognitive deficits: (i) impaired executive functions including working memory and cognitive control deficits, as well as perseverations, (ii) short-term memory deficit, (iii) space and time disorientation, and (iv) language deficits combining impaired lexical access, impaired repetition with a phrase-length effect, and impaired understanding of complex syntactic structures (see Table S7.1) and (iv) parietal symptoms including astereognosia. Examination of motor and primary somatosensory systems was normal. Finally the patient did not present evidence of unilateral neglect in auditory and tactile sensory modalities.

Neurovisual examination showed preserved direct and consensual photomotor reflexes, confirming functionality of retinal and brainstem visual pathways. However, behavioral examination could not reveal any evidence of visual cortical processing: blink to visual threat, optokinetic reflex, visual fixation and pursuit were absent (Naccache, 2018). When presented with visual stimuli, he invariably denied any subjective conscious perception. He could not read any word, letter or number. When engaged on color naming and object naming tasks on visual input, he remained silent and could not produce any correct response. The patient could not perform any of the classical visual tasks related to ventral (word reading, letter reading, digit reading, color naming, object naming, object discrimination) or to dorsal (fixation, saccade orienting, pointing, grasping) visual cortical pathways (see Table S7.2).

Engaged in a forced-choice semantic discrimination task (artefact versus natural object) he performed at chance-level in the visual modality (22/48 correct responses =45.8%; Z-test=-0.58; p-value =0.56), contrasting with an almost perfect performance with auditory input (47/48 correct responses =97.9% vs 50% ; Z-test=6.64 ; p-value < 0.0001). A χ^2 test confirmed the massive difference between these two modalities ($\chi^2=26.6$; p-value <0.00001). The

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semantic knowledge required to perform this task correctly was therefore fully preserved, confirming the perceptual origin of his chance-level performance with visual input.

Structural brain MRI revealed severe bilateral and atrophic lesions of ventral and dorsal pathways in each hemisphere, contrasting with an anatomical preservation of more anterior structures including frontal lobes. Crucially, V1 cortices were partially preserved (see Figure 7.1a).

Figure 7.1

Bilateral severe structural lesions of ventral and dorsal cortical pathways with partial structural preservation of V1

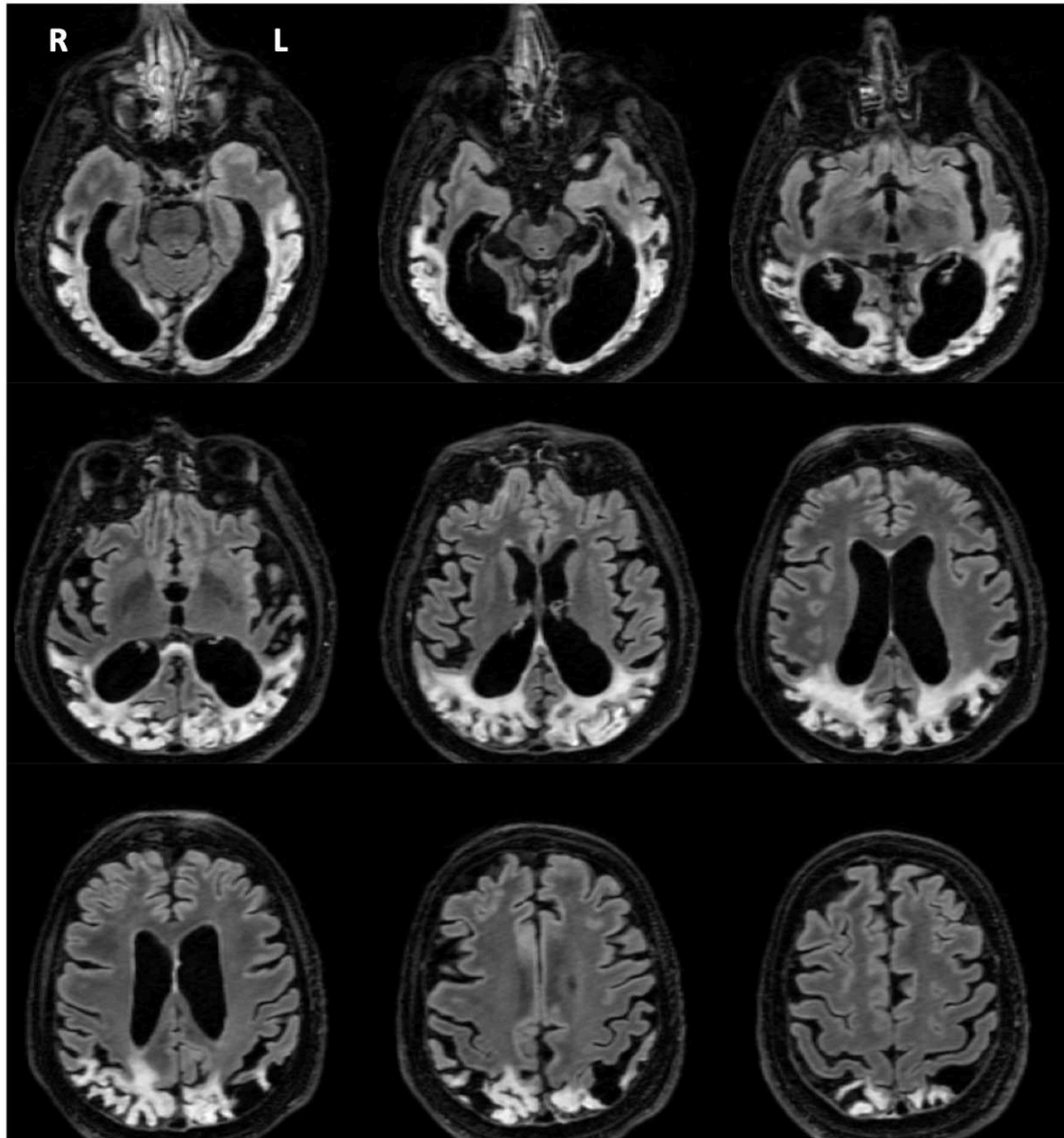


Figure 7.1. Brain axial sections of FLAIR MRI reveal bilateral hyperintensities (in white on the figure) and severe brain atrophy of occipito-temporal (ventral) and occipito-parietal (dorsal) cortical pathways. Crucially, V1 area of each hemisphere appeared partially preserved.

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This unique lesions pattern causing cortical blindness invited us to test the two seminal predictions stemming from Crick and Koch's hypothesis: (Prediction 1) visual stimuli should still activate V1 in this patient lacking conscious vision, and (Prediction 2) functional connectivity between V1 and PFC should be massively impaired, as compared to healthy sighted volunteers.

Electroretinographic recordings first confirmed the normality of retinal processing: P50 and N95 components evoked by visual stimulation of each eye showed normal latencies and amplitudes (Birch, 1992). Recordings of visual evoked potentials (VEP) using the standardized checkerboard procedure revealed the preservation N75 and P100 VEP components that originate from V1 areas (Arroyo et al., 1997; Di Russo et al., 2005; Shigeto et al., 1998). P100 latencies showed a moderate but significant slowdown: 124ms and 122ms respectively after right-eye and left-eye stimulation, versus 107 ± 3.61 ms in healthy male participants of comparable age (Z-scores = 4.24 and 4.79 respectively; both p -value $< 10^{-5}$). N75/P100 peak-to-peak responses showed a non-significant decrease of amplitudes: $3.6 \mu\text{V}$ and $5.8 \mu\text{V}$ respectively after right-eye and left-eye stimulation, versus $8.75 \pm 3.13 \mu\text{V}$ for healthy participants (Z-scores = -1.64 and -0.94 respectively; both p -value > 0.1).

We then scanned the patient with fMRI in order to confirm V1 functionality with a space-resolved technic. He was presented with images from different categories (i.e.: printed words, numbers, faces, houses and tools; see Supplementary Material for details). When contrasting all visual categories versus rest, we found an activation in the left primary visual cortex (MNI -3 -63 -22, $Z=3.78$, $n=17$ voxels), significant only after small volume correction with the primary visual cortex smoothed mask ($p=0.034$ FWE-correction, see Figure 7.2). The reverse contrast (rest $>$ all categories) did not reveal any significant result at the whole brain level, or restricted to the above-mentioned inclusive mask. VEP and fMRI therefore confirmed Prediction 1, by demonstrating unconscious neural activity elicited by visual stimuli in patient's residual V1. Interestingly, the mismatch between normal amplitudes of N75-P100 VEP components on the one hand (that reflect early cortical processing), and reduced amplitudes of V1 fMRI signal on the other hand, is highly suggestive of a lack of recurrent processing between V1 and extrastriate areas - that were massively lesioned in this patient required for V1 sustained activity (Lamme, 2006).

Figure 7.2

Loss of conscious vision associated with V1 activation and impaired functional connectivity with PFC

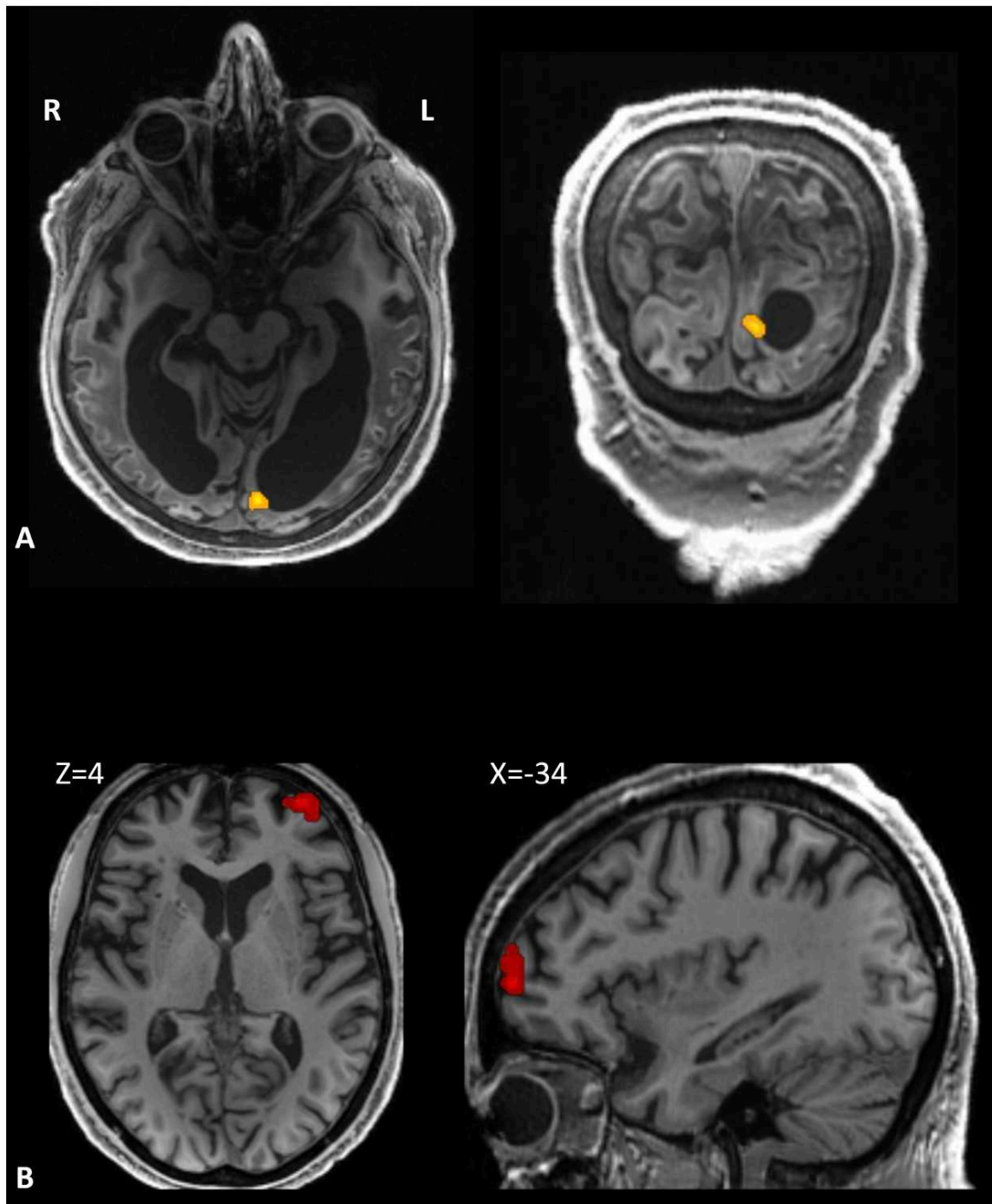


Figure 7.2. (A) Patient's left primary visual cortex (shown in native space) was activated by visual stimuli (voxel $p \leq 10^{-3}$; $p = 0.034$ FWE-correction within V1 inclusive mask).

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(B) As compared to healthy sighted volunteers, patient's V1 area (overlaid on healthy anatomy in MNI space) showed a significant decrease of functional connectivity with a left PFC region previously identified as playing a causal role in conscious vision (Del Cul et al., 2009).

In order to test the V1-PFC disconnection prediction, we then recorded resting-state fMRI. We used as a seed fMRI time-series averaged within V1 inclusive mask defined above, and found a higher connectivity in healthy volunteers as compared to the patient in two regions: right temporal pole (MNI: 16 14 -40) and left anterior prefrontal cortex (MNI: -32 58 4, Z=4.31; see Table 7.1). Crucially, this last PFC region has previously been reported in a lesion study as playing a putative causal role in conscious access to visual stimuli (Del Cul et al., 2009)(MNI -32 54 -6; peak-distance between two studies = 11mm). Importantly, the reverse contrast did not reveal any area that would have been more connected to V1 in the patient than in healthy volunteers.

Table 7.1.

Region	Contrast	Peak coordinates (MNI)	Z value	Cluster size	p-value (cluster-level, FWE corrected)
Right temporal pole	Controls > MG	16 4 -40	4.84	425	<0.001 *
Left anterior prefrontal cortex	Controls > MG	-32 58 4	4.31	190	<0.014 *

* Significant cluster-level P, with voxelwise P<0.001 and clusterwise P<0.05 corrected for multiple comparisons across the whole brain

Table 7.1. Regions more connected to V1 in controls than in the patient during resting-state.

To conclude, we first found that bilateral structural lesions of visual pathways preserving substantial part of V1 cortices induced a state of cortical blindness comparable to bilateral lesions of V1. We then demonstrated that visual stimuli he was not aware of were still processed in patient's V1 areas. Finally, we showed that in healthy volunteers V1 is functionally connected to PFC indirectly through ventral pathways relays, and that this indirect

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V1-PFC connectivity was lost in this patient. These findings strengthen Crick and Koch's hypothesis, and suggest that we are not aware of V1 neural activity inaccessible to PFC.

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My involvement in this work was restricted to the design of the MRI protocol, MRI data acquisition and analysis. I was also able to discuss all the results with Lionel Naccache, and the interpretation of the MRI results. We were able to relate this occipito-frontal connectivity deficit to global neuronal workspace theories, as well as to the connectivity differences found in our synesthete participants.

CHAPTER VIII

General discussion

A. Main results

Our goal was to launch a research program on TTS, with the idea of using this condition as a window into the workings of reading processes and reading acquisition. Beyond its anecdotal aspect, TTS mobilizes the core of reading mechanisms, that is the novel articulation between the visual/orthographic and the auditory/phonological representations of language. We put to light some of the main phenomenological and behavioral features of TTS, and their cerebral correlates, both functional and anatomical.

Phenomenological description. We aimed to better characterize general aspects, as well as to better define the subjective characteristics of TTS. First, consistent with the literature on other synesthesias, we found no significant difference in sex ratio among synesthetes (Simner et al., 2006), associators outnumbered projectors in our group (Amsel et al., 2017; Rouw and Scholte, 2010), and finally, our participants had several other associated synesthesias (Ward, 2013), and other synesthetes in their family. Regarding the subjective description of the phenomenon, all the responses collected from 26 synesthetes show that there is a common base of visuo-temporal characteristics in every participants, with some variability added on. This inter-individual variability is generally described in other synesthesias (Niccolai et al., 2012; Rouw and Scholte, 2010; van Leeuwen et al., 2011). We have also shown that TTS can appear in many circumstances (e.g. when the speaker is out of focus, for one's own speech or thoughts, during film viewing, etc), and that it is not only reserved for real words. Pseudowords, as well as human, animal or object sounds, could trigger it.

Advantages and disadvantages. We then demonstrated that this specificity could be objectified using behavioral tests. We demonstrated an advantage for synesthetes in three tasks involving orthographic working memory with auditory stimulation. When hearing a word, synesthetes were better at counting the number of letters in it, spelling it backwards, or detecting target letters. We failed to show any disadvantage on two visual tasks with auditory interference (lexical decision and letter recognition). The better performance of synesthetes on the first three tasks could be linked to better mental imagery, itself linked to working memory, two processes necessary for the completion of these tasks. Holm et al. (2015) did not report a better ability to spell words backwards, but they had not tested their participants and relied on introspective responses, which are probably not sufficient when it

comes to relatively little effects on error rate and reaction time. The lack of difference in the last two tasks could be linked to the design of the experiments, in which the instruction was to ignore auditory stimulation, with a block design favoring attentional reinforcement during blocks with auditory stimulation. This auditory stimulation, occurring before the visual target in the letter detection experiment, could therefore act as a cue, enabling participants to maximize their attention during this temporal window (Naccache et al., 2002).

Reverse activation of the reading network. In a first stage, we were able to identify in a single synesthete a set of regions activated during TTS, overlapping significantly with his reading network. This network, which we called the TTS network, comprises perisylvian regions involved in language and a ventral occipitotemporal region involved in reading. Dynamic causality analyses also enabled us to demonstrate that word and pseudoword processing during TTS go through two different pathways, fitting in with the two pathways models, with a lexical and a non-lexical pathway (Coltheart et al., 2001; Hickok and Poeppel, 2004). Later, using task-functional MRI in 17 synesthetes and 17 controls, all right-handed, we replicated our results. In synesthetes compared to controls, during TTS, we found left-hemisphere perisylvian regions involved in phonological processing such as the SMG, as well as the VWFA involved in orthographic processing. This network also overlapped with the network activated during reading in synesthetes, supporting our initial hypothesis of a reversed activation of the reading network.

Increased functional connectivity. We also found greater connectivity at rest in synesthetes than in controls, notably between occipital and frontal regions. Our graph-theoretical analyses have shown that the global brain's organization was also different, with more regions being part of the "core" structure in synesthetes than controls. These results are also consistent with our parallel with dyslexia and the disruption of core-periphery organizations in developmental disorders (Sokolowski and Levine, 2023), notably in the context of dyslexia (Finn et al., 2014; Schurz et al., 2015). In TTS, where the orthographic information extracted from phonology is increased, we also find an increased number of regions integrated in the Core structure compared to controls. All the differences found between the two groups are systematically in favor of greater activation or connectivity in the synesthetes. The difference in activation during specific tasks could be a direct reflection of TTS, while the differences in connectivity could be a more global marker of synesthesia.

1. A neural perspective on TTS

Language models

Two-routes model. The stages involved in TTS correspond to those found in language and reading models: the perception of sounds requires the involvement of primary auditory areas located in the superior temporal cortices. The triggering of the phenomenon by both real words and pseudowords or proper nouns reflects the involvement of both lexical and sublexical pathways in TTS. The lexical pathway is thought to be underpinned by the MTG, whose role in lexical-semantic processing is recognized (Binder et al., 2009; Davey et al., 2016; Jedidi et al., 2021), whereas the sublexical pathway is thought to rely primarily on the SMG, whose role in phoneme-grapheme conversion has been described (Roux et al., 2012; Magdalena W. Sliwinska et al., 2015; J.S. Taylor et al., 2013). These two regions are also able to decode between word and pseudoword in our multivariate analyses, supporting the idea of their role in the lexical and sub-lexical pathways of speech processing and reading.

Role of the VWFA and mental imagery. Orthographic visualization during TTS and VWFA activation are thought to be the result of greater mental imagery in synesthetes. Indeed, it is more activated in synesthetes than in controls during TTS. This region is known to be activated during letter and word perception, but activations in the VWFA during mental imagery of words have also been reported (Liu et al., 2023). Synesthetic perceptions are comparable to mental images, being distinct from reality, and indeed synesthetes are known to have greater mental imagery than non-synesthetes when assessed through various questionnaires (K. J. Barnett and Newell, 2008; Price, 2009; Spiller et al., 2015). Furthermore, the vividness of mental imagery seems to correlate with the number of synesthesias (Spiller et al., 2015). However, automatic and spontaneous mental imagery is not specific to synesthesia and can also occur in many circumstances, from simple associative memory (Krans et al., 2013) to various psychiatric disorders such as post-traumatic stress or schizophrenia (Pearson et al., 2013). Dance et al. (2021) have also shown that it is possible to be both aphantasic (without mental imagery) and synesthetic, associative as well as projective. A high level of mental imagery is therefore neither essential nor the only marker of synesthesia.

Overall, our results reinforce the role of the SMG in phoneme-grapheme conversion and sub-lexical processing, that of the MTG in lexical processing and that of the VWFA in mental

imagery of letters. These are all necessary stages in learning to read, and can therefore be a target in rehabilitation.

Links with dyslexia

Similar neural substrates but in opposite directions. Our results reinforce the idea of a parallelism between TTS and dyslexia. Disregarding the different types of dyslexia included, the regions implicated in dyslexia according to several meta-analyses (Linkersdörfer et al., 2012; Maisog et al., 2008; Paulesu et al., 2014; Richlan et al., 2011, 2009) are largely superimposable with those identified in our TTS network. These regions are generally under-activated in dyslexia compared with controls, whereas they are over-activated in TTS. In terms of connectivity, we generally find decreases in functional (Finn et al., 2014; Yu et al., 2022) and structural (Sihvonen et al., 2021; Vanderauwera et al., 2017) connectivity in dyslexia, whereas we found increases in connectivity in TTS, at rest or for psycho-physiological interaction analyses. These increases in activation and connectivity are consistent with an excess of "top-down" influence of speech networks on reading networks during TTS.

In some dyslexias, the lexical or sub-lexical pathway is disrupted. As synesthesia can be trained (Colizoli et al., 2014; Rothen et al., 2018), we can therefore imagine focusing rehabilitation in these dyslexias on strengthening and automating phoneme-grapheme conversion in order to train TTS in these patients. Strengthening the "top-down" influences of speech networks on reading networks could reinforce lexical and sub-lexical pathways, and thus enable optimization of rehabilitation in these dyslexias.

2. Relationships with theories of synesthesia

Predisposition to synesthesia. According to Ward (2019), synesthesia is a binary phenomenon, quite distinct from the typical neurocognitive spectrum, but occurring on a **predisposed terrain**, which is itself continuous. Synesthetes share certain characteristics, whether cognitive such as mental imagery (Spiller et al., 2015), creativity (Chun and Hupé, 2016; Rothen and Meier, 2010) or memory (Ward et al., 2019), neural such as connectivity, or genotypic. These characteristics would predispose them to synesthesia, but are neither necessary nor sufficient, and would indeed be the hereditary part of synesthesia, rather than a specific type of synesthesia. Indeed, members of families of synesthetes may share some of

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these characteristics without being synesthetes (Colizoli et al., 2017; Ward, 2019). Synesthesia would therefore result from 1/ a predisposing terrain and 2/ a random component, weighted by the degree of predisposition. The degree of predisposition would therefore be correlated with the probability of being synesthete, phenomenological variability and the number of synesthesias (Figure 8.1, Ward, 2019). In our study, functional connectivity at rest in synesthetes (measured by global correlation), tended to correlate with the number of synesthetes. In contrast, increased occipito-frontal connectivity was not correlated with the number of synesthesias. As the type of synesthesia developed is rather random according to Ward (2019) and linked to brain architecture among other things, this occipito-frontal connection could therefore be a more or less specific marker of TTS.

Figure 8.1

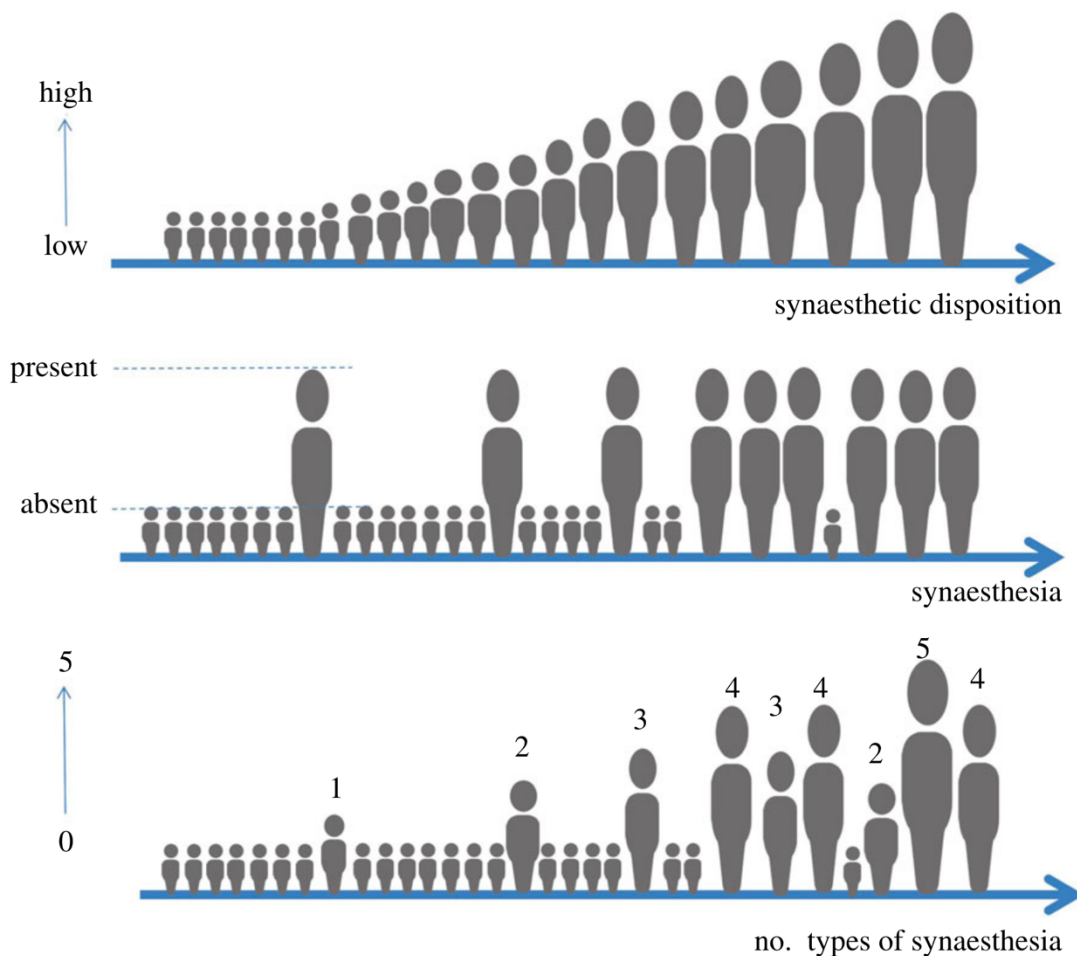


Figure 8.1. Relationship between predisposition to synesthesia, existence of synesthesia and number of synesthesias. The 1st line shows the continuum of predisposition to synesthesia in the population. The 2nd line shows the existence or non-existence of synesthesia, which is a stochastic phenomenon, but correlated with predisposition. This line shows that a person with a weak predisposition can be a synesthete and vice versa. The 3rd line shows the number of synesthesias, which is also correlated with predisposition.

Adapted from Ward (2019).

Difference in conscious access. Another explanation for synesthesia could be related to conscious access to information. Primary activations would be the same in synesthetes and non-synesthetes, but information would not be propagated in the same way. In people with aphantasia, a decrease in connectivity between the region responsible for visual mental imagery (Fusiform imagery node, FIN) in the left vOTC, and the fronto-parietal networks during visual mental imagery and perception has been shown, despite similar performance in behavioral tests (Liu et al., 2023; Liu and Bartolomeo, 2023). Another study also showed a decrease in resting-state connectivity, this time between the prefrontal cortex and the visual occipital cortex (Milton et al., 2021). According to Global Neuronal Workspace models (Dehaene et al., 2006; Mashour et al., 2020), this reduced connectivity could be responsible for the lack of awareness of their experience of visual imagery. In a similar way, synesthetes could have a greater awareness of certain information coming from primary sensory areas, and this would be reflected by the increase in occipito-frontal connectivity at rest in our study. The results of our study of the patient with lesions of the visual associative areas, and the work of Del Cul et al (2009) also point in the direction of a role for this frontal region and its connectivity to the occipital regions in the awareness of visual information. In our patient's case, it is a decrease in connectivity between two regions that is responsible for a decrease in conscious access to visual information, whereas it could be the opposite in synesthesia (Rothen and Terhune, 2012).

Global neuronal workspace (GNW) model. This model states that consciousness results from an extended neural network (Dehaene and Naccache, 2001). There are a number of modules in charge of a specific task, such as vision or hearing. The information they process is only

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consciously accessible, and therefore reportable to the first person, after being integrated into a global workspace, including in particular the fronto-parietal regions (Baars et al., 2021; Deco et al., 2021), whose properties of dense connectivity within this high-level network account for both the uniqueness of conscious content at a given moment, and the property of cognitive availability (Baars, 1993; Dehaene et al., 1998; Dehaene and Naccache, 2001; Mashour et al., 2020). In the context of synesthesia, one explanation would be that information would be propagated more extensively in the concurrent module, due to a specific increase in connectivity with this module, whether functional and/or structural, and we would therefore have a more or less real perception in this modality. In our functional MRI study, we showed stronger activation in the VWFA during language listening. This region is activated by spoken language in non-synesthetes under the influence of top-down connections (Yoncheva et al., 2010), which may fit in with the propagation of information in the GNW model, but it becomes even more active in TTS, suggesting even more top-down connectivity. We have also shown an increase in functional connectivity between primary auditory areas and the VWFA during language listening, which could reflect this over-propagation of auditory information once conscious to the orthographic processing module, reflected by greater synchronization between these areas.

Environmental influences. Synesthetic associations and their characteristics are influenced by the environment and learning, whether in relation to repeated exposure (Witthoft and Winawer, 2006), or more lexical-semantic associations (Simner et al., 2005; Ward and Simner, 2003). In our phenomenological study, participants report certain aspects that can be influenced in the same way. For example, synesthesia generally appears as subtitles in their visual field (centered in the bottom), probably inspired by the position of subtitles in the majority of films. Synesthetic perception can also appear as a speech bubble close to the speaker's mouth, as dialogue is often depicted in comic strips. For some, subtitles also scroll like a teleprompter, from right to left. Figures and numbers are perceived according to context, in a way that is adapted to their usual format in our society. Also, for some of our participants, certain sounds are represented as onomatopoeia, in the same format as they are in popular culture. Most people are exposed to these representations, but do not develop synesthesia. This exposure is not linked to the development of synesthesia, but merely serves as a model on which it is built.

Learning aid. We can also imagine synesthesia as an aid to learning. Indeed, the substrates of synesthesia are often culturally learned sequences (days of the week, months of the year, numbers, letters, etc.), more or less concrete (Witthoft and Winawer, 2013). The association of colors with numbers and letters, or the use of spatial representations to categorize the months of the year (Price and Pearson, 2013) helps facilitate this learning, and could therefore explain such a prevalence of these sequences among inducers. Thus, the main benefit reported by our participants is the impression of better spelling; systematic orthographic visualization of a heard word may therefore help acquire this better spelling. On the contrary, this ability could be a consequence of synesthesia, rather than the other way round. This ambiguity also exists for most traits associated with synesthesia, such as enhanced sensory perception, creativity or mental imagery (Ward, 2019). If synesthesia facilitates learning, we could therefore imagine a higher prevalence among students with learning difficulties. However, Basirat and Hupé (2020) wanted to test the existence of such a link, but showed no difference in the prevalence of synesthesia among students with writing disorders.

3. Limits and futures directions

Limits

Our study has a number of limitations.

No diagnostic test. Firstly, our participants were self-referred synesthetes. Since synesthesia is a perceptual specificity, it is mainly subjective. With regard to TTS in particular, which has been little studied, there is no diagnostic test available such as those used in other synesthesias (Carmichael et al., 2015; Eagleman et al., 2007). We tried to identify as best as we could the manifestations of synesthesia in each participant in order to ascertain the nature of the phenomenon, and we were also able to objectify a behavioral advantage during certain tests, which should enable us to develop some diagnostic tools.

Study size. The other main limitation of our work concerns the small size of the functional MRI study. As previously mentioned, small headcount is one of the main limiting factors of previous functional MRI studies in synesthesias (Hupé and Dojat, 2015). This limited size is related to the relative rarity of TTS synesthetes, but did not prevent us from showing differences in activation and connectivity, highlighting the differences between groups. We

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are continuing to recruit new subjects on an ongoing basis, with new acquisitions, which should reinforce these initial results.

Studies in progress

Structural connectivity. Among the acquisitions still in progress, we have a diffusion sequence to analyze the structural connectivity of these participants. It is not yet clear whether synesthesia is linked to an increase in structural or functional connectivity (Hubbard and Ramachandran, 2005). It is also known that functional and structural connectivity are correlated (Babaeeghazvini et al., 2021) and that through Hebbian mechanisms, functional connectivity can influence structural connectivity. Consequently, only a longitudinal study in children before and after learning to read would make it possible to identify what neuronal specificity exists in TTS synesthetes and whether it is possible to identify predispositions.

Length manipulation task. We also have another experiment in the pipeline, in which we present our participants with a set of stimuli, both visually and aurally. These stimuli vary in orthographic and phonological length: they can be phonologically and orthographically short, long in both modalities, or phonologically short and orthographically long. We aim to demonstrate a greater orthographic length effect during auditory stimulation in synesthetes than in controls, as well as to compare other effects in the different modalities. Given a higher perceptual capacity in synesthetes (Ward, 2019), we could also observe differences in phonological length effect during auditory presentation or orthographic effect during visual presentation.

Better temporal resolution. As MRI has poor temporal resolution, our results do not allow us to judge the sequence of activation of the different regions identified in TTS. To this end, in collaboration with Ladislav Nalborczyk, a post-doctoral fellow in the team, we will shortly be starting a magnetoencephalography (MEG) protocol with auditory stimulation, in synesthetes and controls.

New avenues to consider

New tests. Firstly, it is important to develop diagnostic tests as previously specified. We would also like to investigate the need for conscious access to auditory stimuli in TTS to generate corresponding subtitles, which appears to be the case (Edquist et al., 2006; Rich and

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Mattingley, 2003). In TTS, this could be achieved by manipulating the signal-to-noise ratio of the stimuli, or by using ambiguous auditory stimuli, for example. In the idea of a predisposing condition for synesthesia, it might also be interesting to administer behavioral tests and MRI sequences to families of synesthetes, in order to differentiate between predisposing and TTS-specific markers.

Stimulation. We have identified a number of regions activated during synesthesia, but it would be interesting to be able to identify the causal link between these activations and the phenomenon: we can imagine that certain regions would be responsible for certain aspects only of TTS, or on the contrary that inhibition of a single region could completely suspend TTS. To achieve this, we could use a TMS (Murakami et al., 2013) protocol, as already carried out in GC synesthesia, for example (Muggleton et al., 2007; Muggleton and Tsakanikos, 2013).

Hypnosis. Cases of hypnosis-induced synesthesia have been reported (Cohen Kadosh et al., 2009), although these are not in all respects identical to developmental synesthesia (Anderson et al., 2014). Because of the hypnosis expertise of collaborators in our team, hypnotic induction of TTS could be performed, and measured by behavioral tests but also by connectivity imaging measurements, where participants would be their own controls. Hypnosis acts by modulating functional connectivity between certain cortical regions (Demertzi et al., 2011; Jiang et al., 2016). Linking the mechanisms of hypnosis to models of the global neuronal workspace, some of our collaborators (unpublished work) postulate that a person's suggestibility could be correlated to a greater influence of global workspace neurons on a given cortical module, in connection with a greater membership of neurons from that module in the global neuronal workspace. This mechanism is reminiscent of the one previously mentioned concerning synesthesia within the global neuronal workspace, and it would therefore be interesting to study the link between hypnotic suggestibility and the existence of one or more synesthesias

1. Morphometry

Several authors have reported structural and morphometric particularities in synesthetes (Hänggi et al., 2011; Jäncke et al., 2009). It is also known that there is a probable genetic origin to synesthesia in general, and that certain morphometric markers are influenced by development and therefore genetics (Panizzon et al., 2009; Strike et al., 2019). We therefore wanted to compare these parameters in the context of TTS. This part of the work was mainly carried out by Romain Labhari, then a Master 2 student in the team, under the main supervision of Laurent Cohen, and more indirectly my own.

We carried out quantitative analyses, comparing the volume, area and thickness of the cortex across the whole brain, as well as qualitative analyses, comparing sulcus configurations in different cortical regions.

A. Methods

Participants

Our inclusion and exclusion criteria were the same as before: age at least 18, report having TTS synesthesia, and have no neurological or psychiatric history. Our research was approved by the INSERM Institutional Review Board (protocol C13-41), and all participants gave their informed consent. In all, we recruited 26 synesthetes and 26 controls, including 5 left-handers in each group.

Acquisition

Images were acquired as described above. We used a Siemens 3T MAGNETOM Prisma MRI. T1-weighted images were acquired with the following parameters: TR/TE/flip angle = 2400 ms / 2.23 ms / 9°, and voxel size = 0.7 × 0.7 × 0.7 mm. We used a 64-channel antenna.

Analyses

Pre-processing. For quantitative analyses, we used CAT12 (<http://www.neuro.uni-jena.de/cat>) only to apply a bias correction. For the other preprocessing steps, we used

Appendix: Morphometry

Freesurfer version 7.3.2 (<https://surfer.nmr.mgh.harvard.edu/>). The initial pre-processing stage included a large number of steps, in particular, segmentation of the anatomy used to delimit the white, the grey matters and the subcortical structures. A mesh of triangles was applied on the junction between the grey matter and the pia and defined the “white” surface. This surface was then expanded towards the cerebrospinal fluid to create the “pial” surface. In a second step, the surfaces were inflated in two stages to a sphere, which was registered to a template sphere (normalization). Different measures (area, thickness, volume) were then transferred to the target sphere model with some adjustments for area and volume, to avoid the total value to change between the source sphere and the target one. The next step was the cortical parcellation, allowing to label each cortical area. Then smoothing (6mm FWHM) was applied for group comparison purposes, and maps were concatenated for vertexwise analysis.

The segmentation step was checked visually and corrected manually where necessary for all subjects.

For qualitative analyses, we used BrainVISA version 5.1.0 (<https://brainvisa.info/web/>), which performs skull bone removal and tissue segmentation. There is no image normalization to ensure that sulcus analyses are as reliable as possible. Next, the sulci are segmented. Finally, classification of each sulcus of interest is performed manually and blinded to the participant's group.

Measurements. For quantitative analyses, we were interested in several measures: cortical thickness, cortical area, cortical curvature, and cortical volume.

The **cortical thickness** at a vertex is defined as the distance between the white and pial surfaces at that vertex (Fischl and Dale, 2000; Greve and Fischl, 2018). The **area** of a vertex is defined as the average area of the triangles forming the vertex (Delalande et al., 2020). The **cortical curvature** is calculated for each vertex of the white surface as the inverse of the radius of an osculating circle of that vertex (King et al., 2016). The **cortical volume** is roughly defined as the area times the thickness (Winkler et al., 2018).

Student's t-tests were then performed to compare these different measures between the 2 groups, including age as a covariable.

Appendix:
Morphometry
Results

For the quantitative analyses, we identified a greater cortical volume in controls compared to synesthetes in the posterior part of the left superior temporal sulcus (STS), extending to the left SMG (**Figure 9.1A**, vertex threshold $p < 0.001$, cluster threshold $p < 0.05$). There was no significant effect of manual dominance and no interaction of synesthesia and dominance. As the cortical volume decreases with age (Lemaitre et al., 2012), we did a sanity check and looked at the age effect. We found an effect of age on three left frontal regions, in which the cortical volume was inversely correlated to the age (**Figure 9.1B**).

Figure 9.1

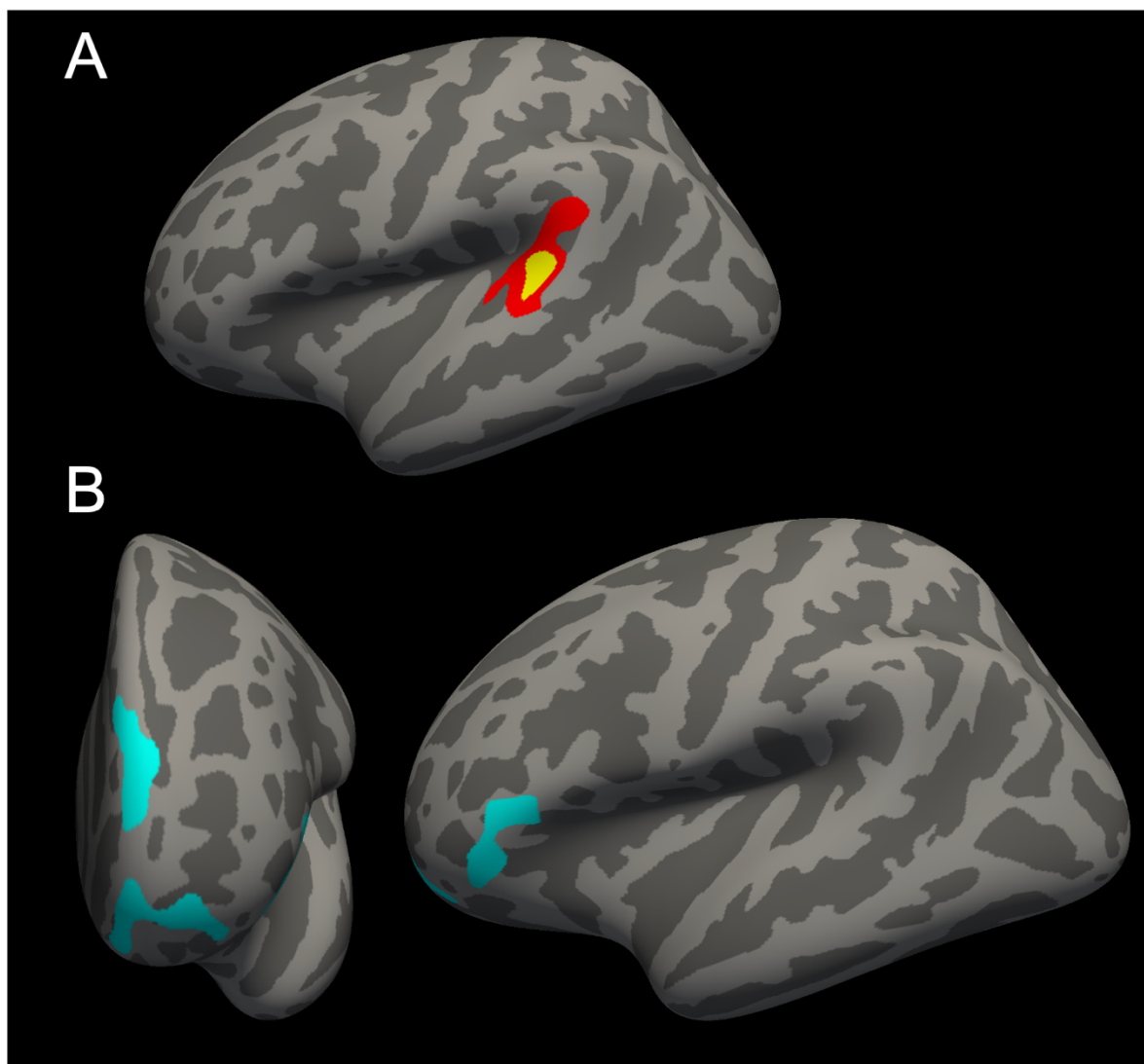


Figure 9.1. Cortical volume. (A) Lateral view of the inflated surface of the left hemisphere. When comparing synesthetes < controls, we found a higher cortical volume in the left STS and

SMG in controls. Voxels with a p-value < 0.01 are in red, voxels with a p-value < 0.001 are in yellow. Both clusters shown, with different voxelwise p-value are thresholded at $p < 0.05$. (B) Anterior and lateral views of inflated surface of the left hemisphere. We show three frontal clusters, two infero-lateral and one medial, which are inversely correlated with age: as age increases, cortical volume in these areas decreases. Voxelwise $p < 0.001$, clusterwise $p < 0.05$.

We found no difference for the other measures.

As regards qualitative analyses, only the sulcal pattern of the anterior cingulate cortex has been analyzed and shows no difference between the 2 groups. The temporo-parietal junction and ventral sulcus have not yet been analyzed.

Discussion

We showed that there were differences in cortical volume, with a greater volume in controls with regard to the STS and SMG on the left. Variability in cortical volume is more likely attributable to variability in surface area (Im et al., 2008). Surface area is influenced by the cortical folding (Garcia et al., 2018), which is linked to the connectivity and development (Mota and Herculano-Houzel, 2012). Consequently, it is interesting that we found a difference precisely in regions identified as involved in TTS, although the direction of the difference is unexpected. Previous studies using morphometry in synesthetes showed opposite results from ours (Jäncke et al., 2009). Our results could therefore only suggest a connectivity difference in this area between groups, that might be caused by an enhanced long-range and reduced short-range connectivity in synesthetes. Further sulci configuration analyses in this area could help interpretation of our results, providing further evidence with sulci differences.

Our small group size could be a reason for the lack of difference on surface area and cortical thickness in our participants. Further morphometric analyses should be computed with more participants.

2. Supplementary material

A. Chapter II: A single case neuroimaging study of tickertape synesthesia

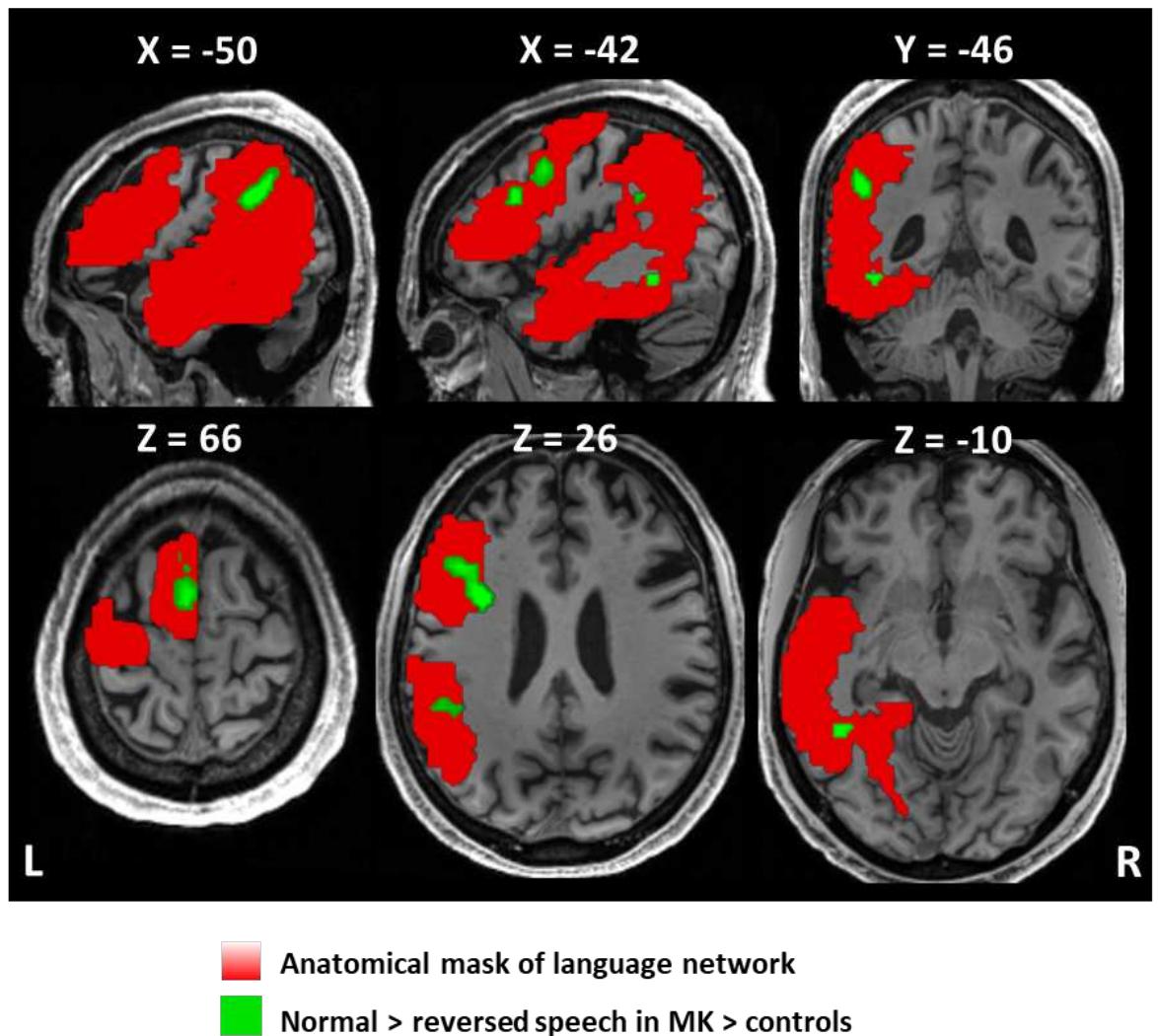
- Supplementary Figure S2.1

Appendix:

Supplementary material

- Supplementary Figure S2.2
- Supplementary Figure S2.3
- Supplementary Figure S2.4
- Supplementary Figure S2.5
- Supplementary Figure S2.6
- Supplementary Table S2.1
- Supplementary Table S2.2

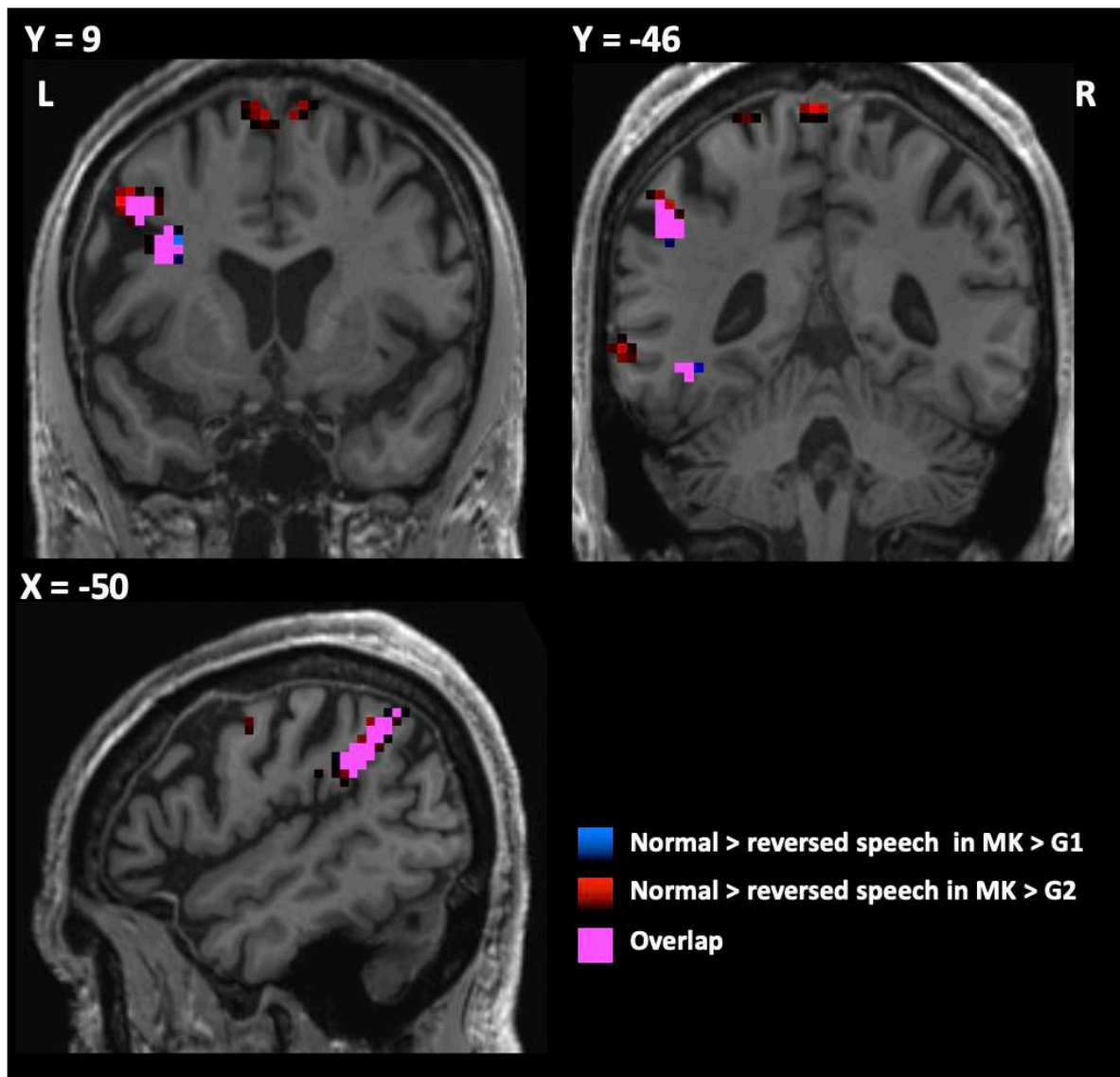
Supplementary Figure S2.1



For some analyses of **Experiment 1**, we defined a broad region of interest covering left-hemispheric language areas and VOT cortex (red), by merging the opercular and triangular parts of the inferior frontal gyrus, the supplementary motor area, the precentral, fusiform, inferior parietal, supramarginal, angular, superior and middle temporal, and inferior temporal gyri, as defined in the AAL 3 atlas (Rolls et al., 2020). The “TTS network” (green) was included in this broad region of interest.

Supplementary Figure S2.2

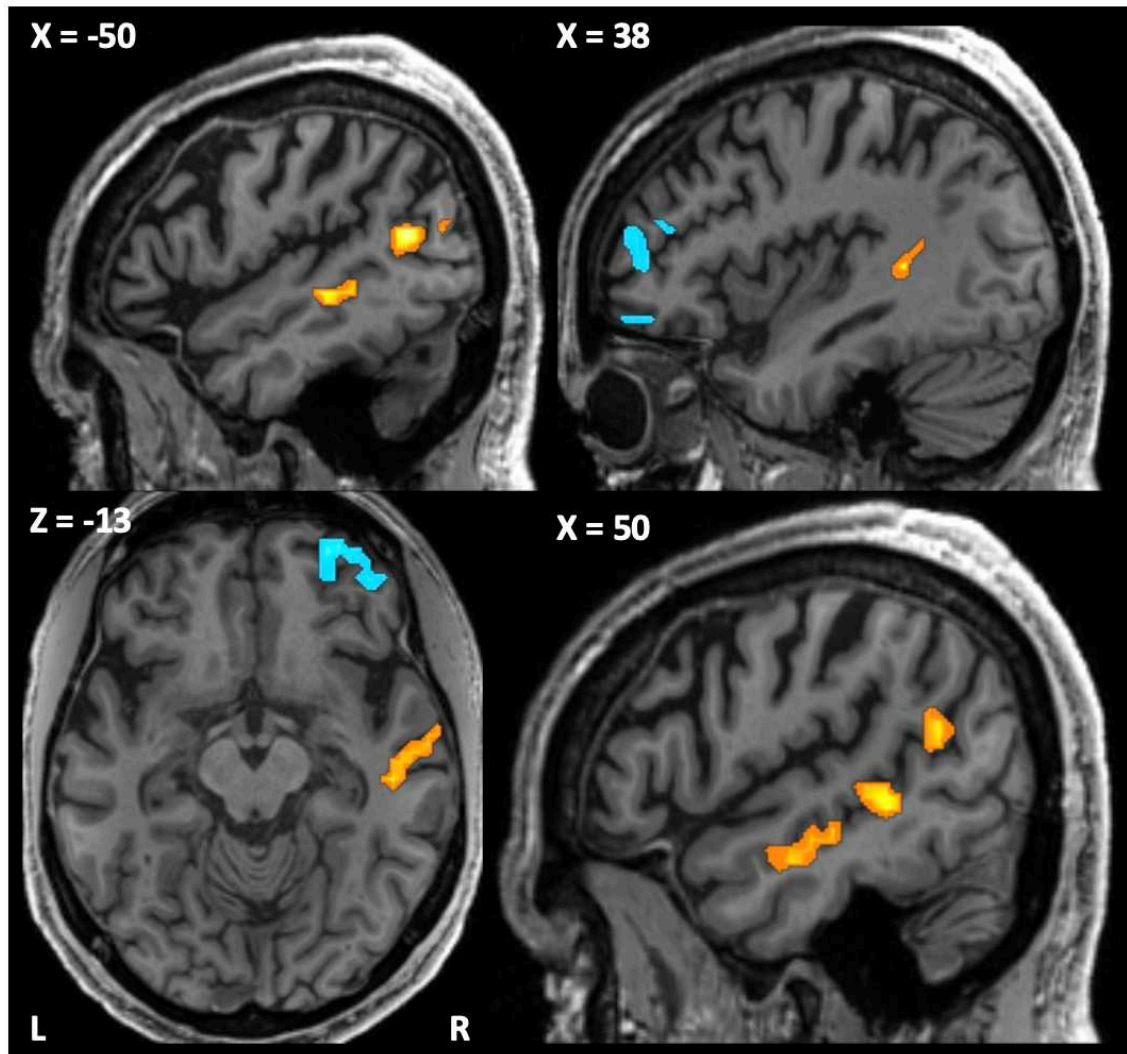
Reproducible differences between MK and the two groups of controls for the contrast “normal > reversed speech”



The main differences between MK and controls were remarkably replicated across separate comparisons of MK > G1 (red) and MK > G2 (blue), which overlapped in the left SMG, IFG and VWFA (magenta).

Supplementary Figure S2.3

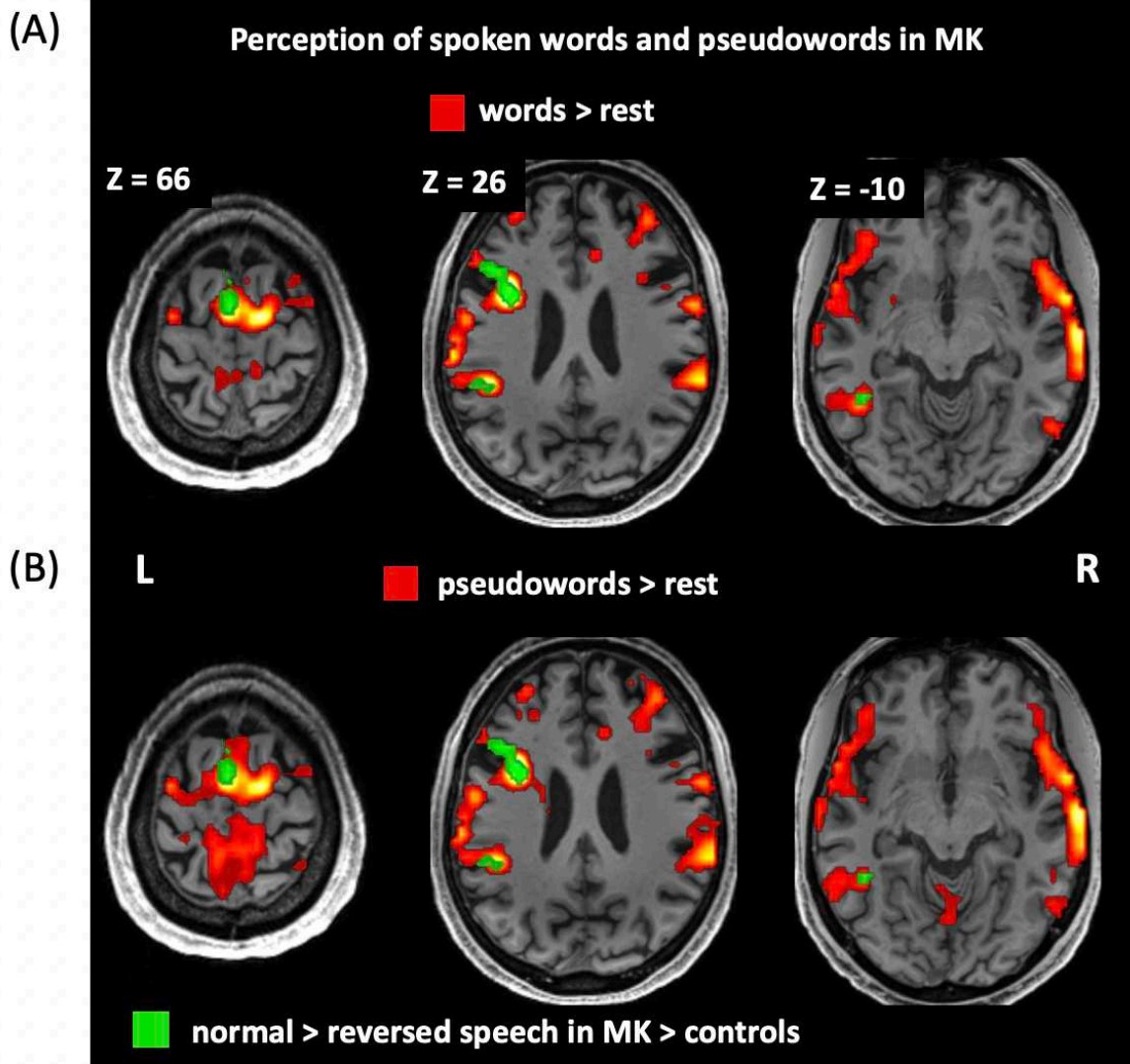
Comparison between the two groups of controls
for the contrast “normal > reversed speech”



- Normal > reversed speech in G2 > G1
- Normal > reversed speech in G1 > G2

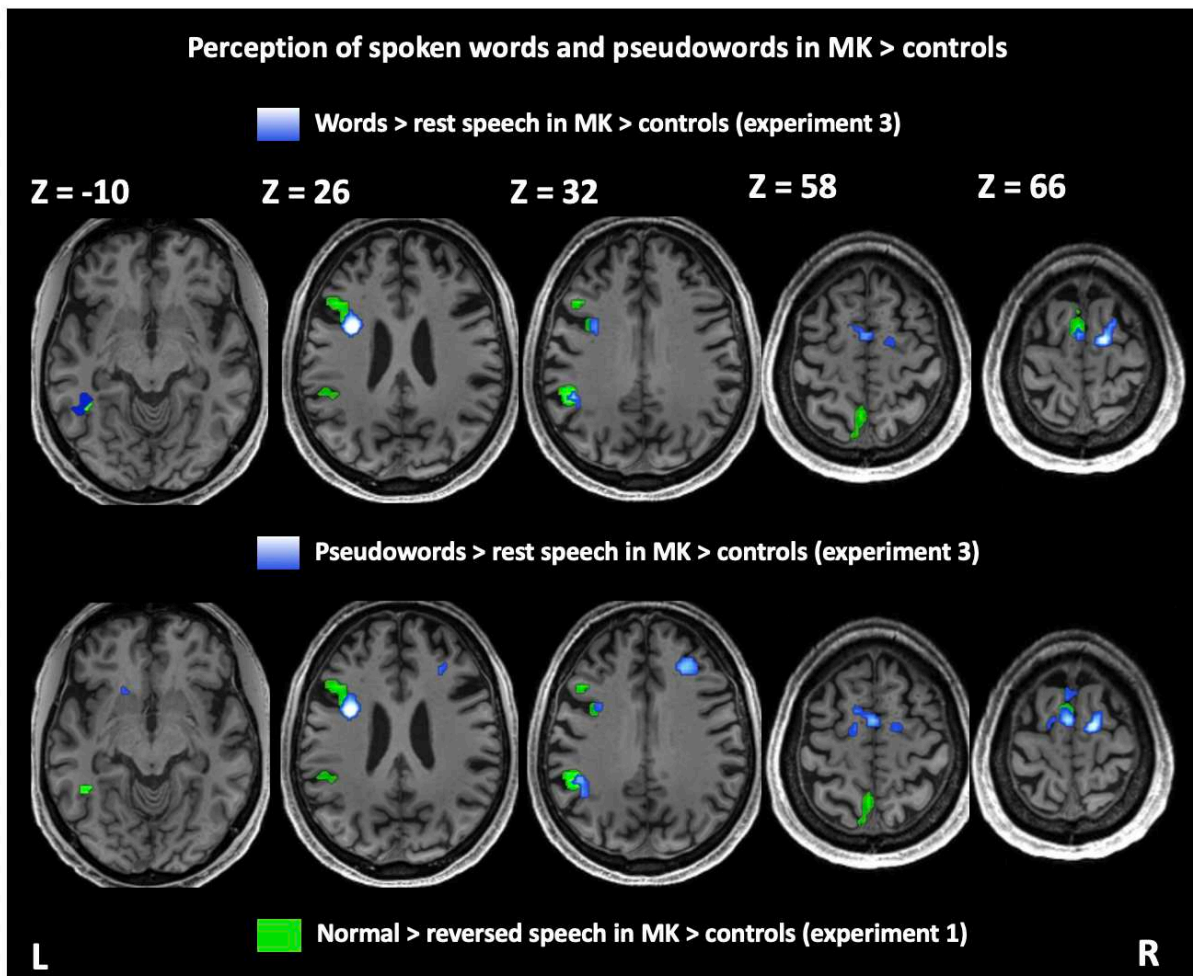
There were stronger activation for G1 > G2 in bilateral superior temporal sulci (STS, hot colors), and stronger activation for G2 > G1 in the right prefrontal cortex (blue). Those regions had no overlap with the areas distinguishing MK from controls.

Appendix:
Supplementary material
Supplementary Figure S2.4



In **Experiment 3**, words and pseudowords triggered tickertape synesthesia (TTS) in MK. Activated regions for spoken words (A) and spoken pseudowords (B) relative to rest (hot colors) are essentially identical irrespective of lexicality, and encompass areas over-activated in MK during TTS in Experiment 1 (green). (C)

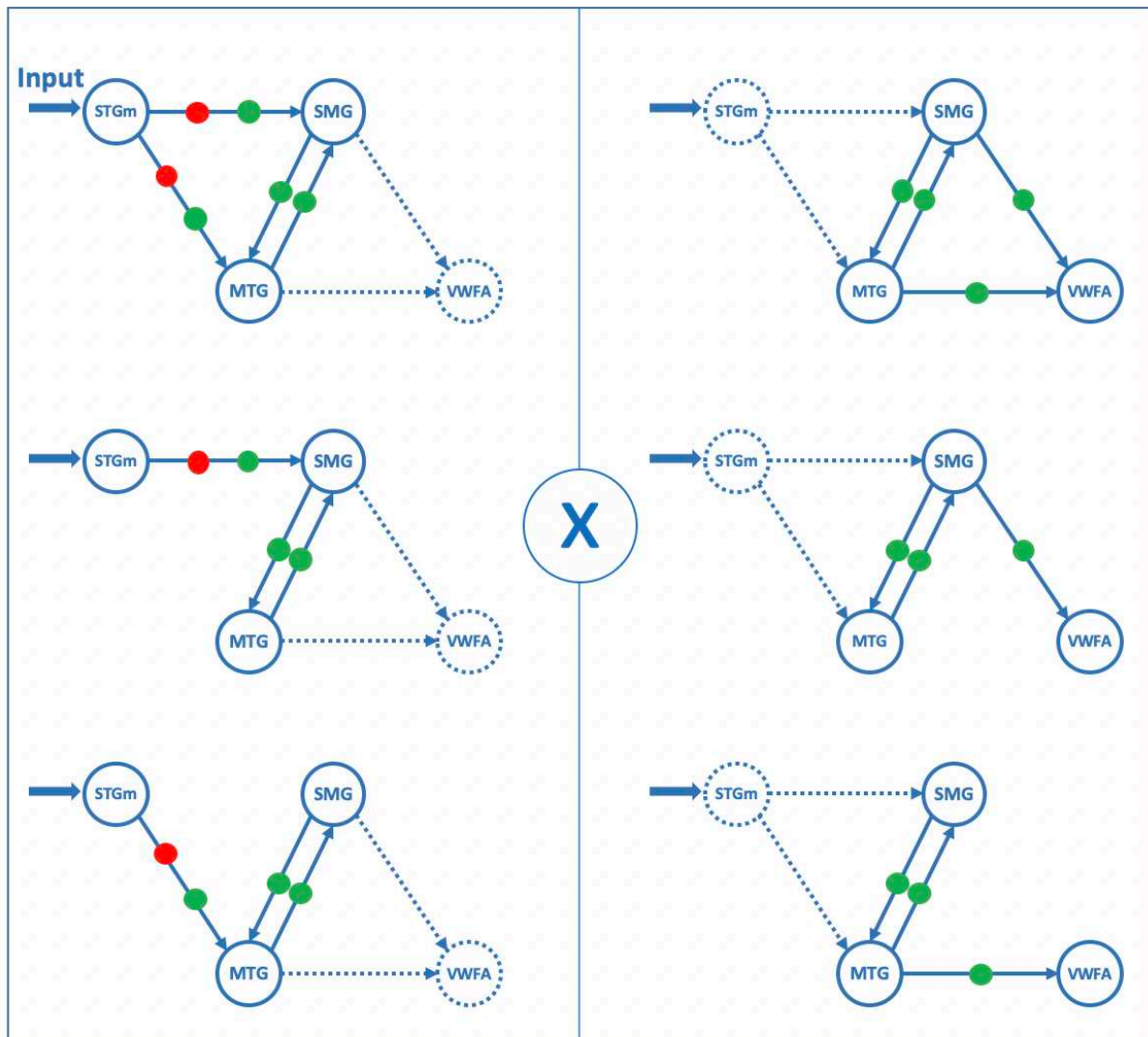
Supplementary Figure S2.5



In **Experiment 3**, both spoken words and pseudowords triggered TTS in MK. The comparison of MK minus controls for the contrasts words > rest (top row) and pseudowords > rest (bottom row) revealed overactivation in MK's TTS network (blue), in regions overlapping with those observed in Experiments 1 (green) and Experiment 2 (see Figure 3).

Appendix:
 Supplementary material
Supplementary Figure S2.6

Model families and modulations for Dynamic Causal Modelling



Model families and modulations for Dynamic Causal Modelling. All auditory stimulations drive the model through the STG (thick arrow), the SMG implements the phonological route, the MTG the lexical route and the VWFA the orthographic output. The STG drives unidirectionally the SMG, the MTG or both (3 options depicted by solid arrows in the left panel). The SMG and MTG are always reciprocally connected, implementing the interaction of the phonological and lexical routes. The VWFA receives unidirectional input from the SMG, the STG, or both (3 options depicted by solid arrows in the right panel). Combining the 3x3 options results in 9 possible families of structural models. Red dots show allowed modulations by the contrast of normal vs reversed speech (Experiment 1). Green dots show allowed modulations by the contrast of real vs pseudowords (Experiment 3).

Supplementary Table S2.1.

Experiment 1: Regions activated in controls when listening to reversed speech, and to normal > reversed speech.

Reversed speech > rest				Normal > reversed speech			
Region	Peak coordinates (MNI)	Z-score	Cluster-size	Region	Peak coordinates (MNI)	Z-score	Cluster-size
Left STG	-48 -16 5	>8	1263	Left STS	-54 5 -16	7.56	4195
Right STG	51 -16 8	>8	1318	Right STS	48 14 -22	6.40	
Right mesencephalic pedunculus	18 -25 -4	5.21	42	Left SMA	-39 11 53	5.32	96
Right postero-inferior frontal gyrus	42 11 20	5.16	211	Right inferior frontal	54 26 5	4.76	50
Right SMA	51 2 50	4.71	51	Bilateral precuneus	-6 52 38	4.73	177
Left postero-inferior frontal gyrus	-33 14 29	4.04	48	Left medial SMA	-6 5 65	4.52	50
				Bilateral orbitofrontal cortices	0 59 -16	4.35	38

MNI, Montreal Neurological Institute; STG, Superior temporal gyrus; SMA, Supplementary motor area; STS, Superior temporal sulcus.

Appendix:
Supplementary material

Supplementary Table S2.2.

Experiment 2: Regions showing preferential activations for categories of visual stimuli.

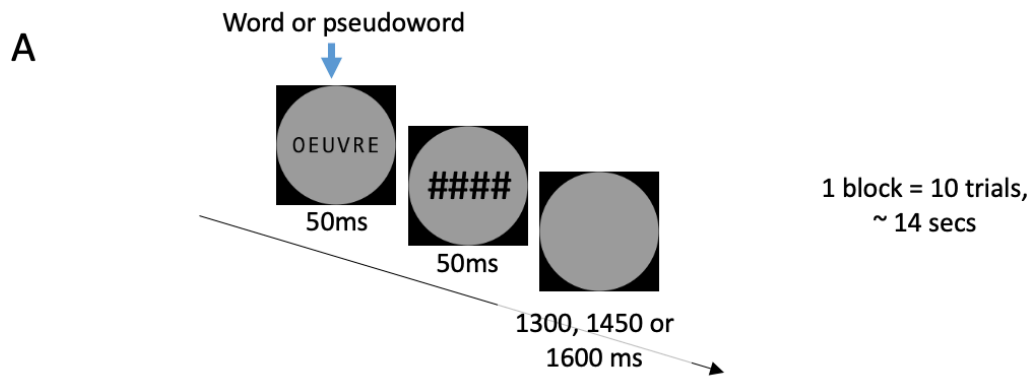
Contrast	Region	Peak coordinates (MNI)	Z _{max}
Words > Houses and Faces	Left STG	-63 -22 5	> 8
	Left fusiform gyrus	-45 -52 -10	> 8
	Right STG	69 -31 11	7.71
	Left inferior frontal gyrus	-33 8 23	6.85
	Left supramarginal gyrus	-48 -40 32	6.29
	Left precuneus	-9 -73 59	4.72
	Right cuneus	12 -97 14	4.6
	Left SMA	-6 8 62	4.43
	Faces > Houses and Words	Right peristriate area	51 -70 -1
Right fusiform gyrus		42 -55 -13	5.44
Houses > Faces and Words	Right visual association area	30 -88 8	> 8
	Left visual association area	-33 -85 23	> 8
	Left parahippocampal gyrus	-30 -37 -16	> 8
	Right parahippocampal gyrus	30 -49 -10	6.09
Tools > (Words, Houses and Faces)	Left lateral occipital cortex	-42 -67 2	> 8
	Right lateral occipital cortex	45 -64 -4	> 8
	Left fusiform gyrus	-30 -49 -13	5.08
Bodyparts > (Words, Houses and Faces)	Right lateral occipital cortex	45 -64 -4	> 8
	Left lateral occipital cortex	-42 -67 2	> 8
	Left fusiform gyrus	-30 -52 -13	5.1

MNI, Montreal Neurological Institute; STG, superior temporal gyrus; SMA, supplementary motor area.

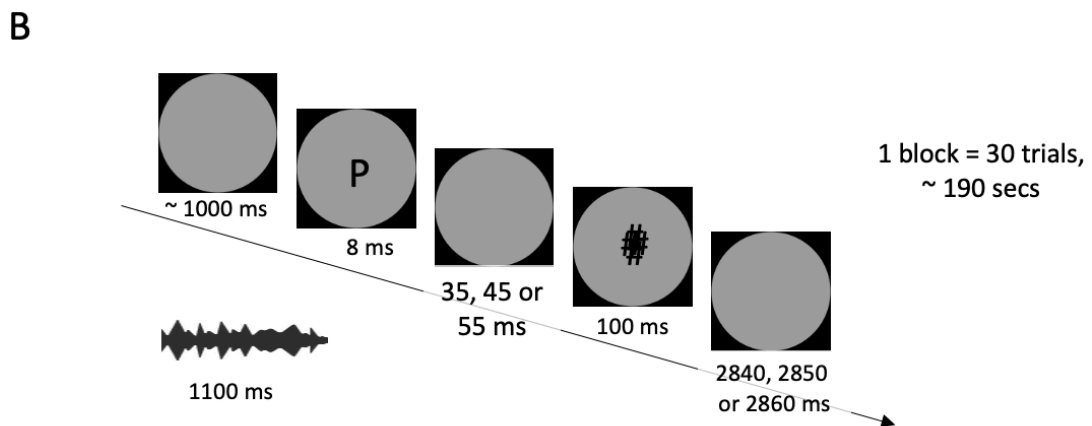
B. Chapter IV: Advantages and disadvantages of TTS

- Supplementary Figure S4.1
- Supplementary Figure S4.2

Supplementary figure S4.1



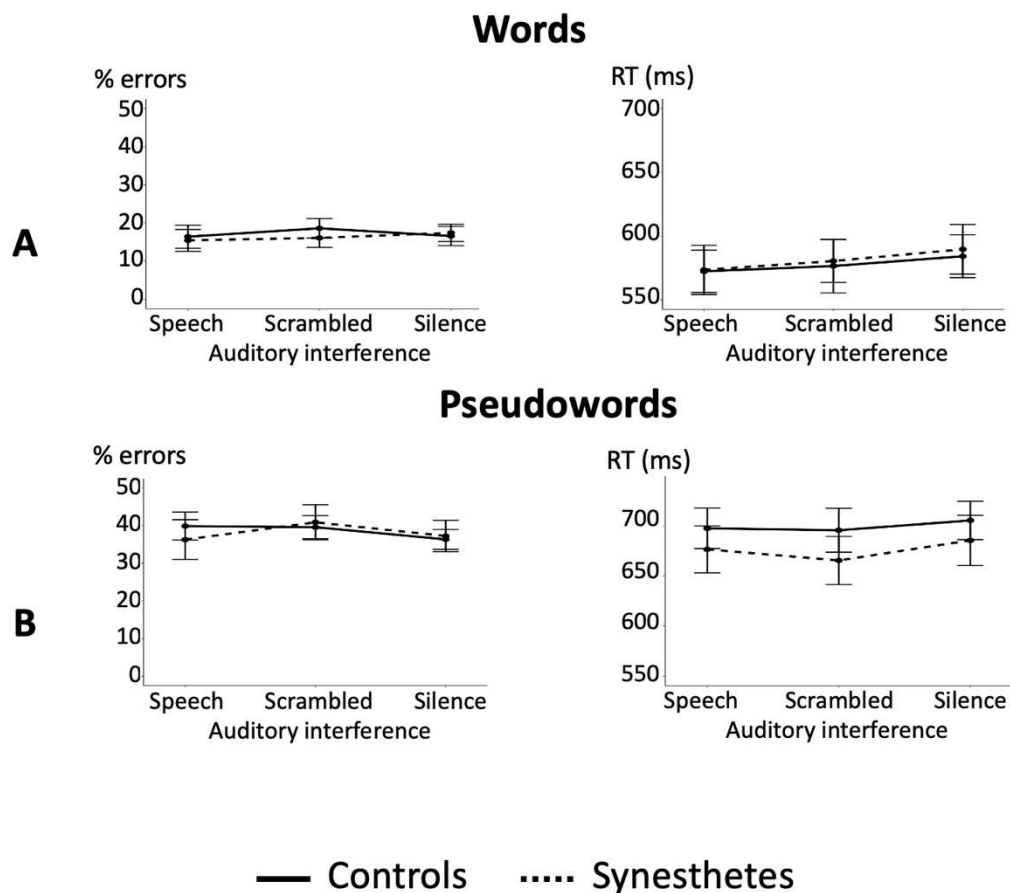
Temporal structure of trials in Experiment 4 (lexical decision)



Temporal structure of trials in Experiment 5 (letter detection)

Supplementary figure S4.2

Interference of speech on visual lexical decision



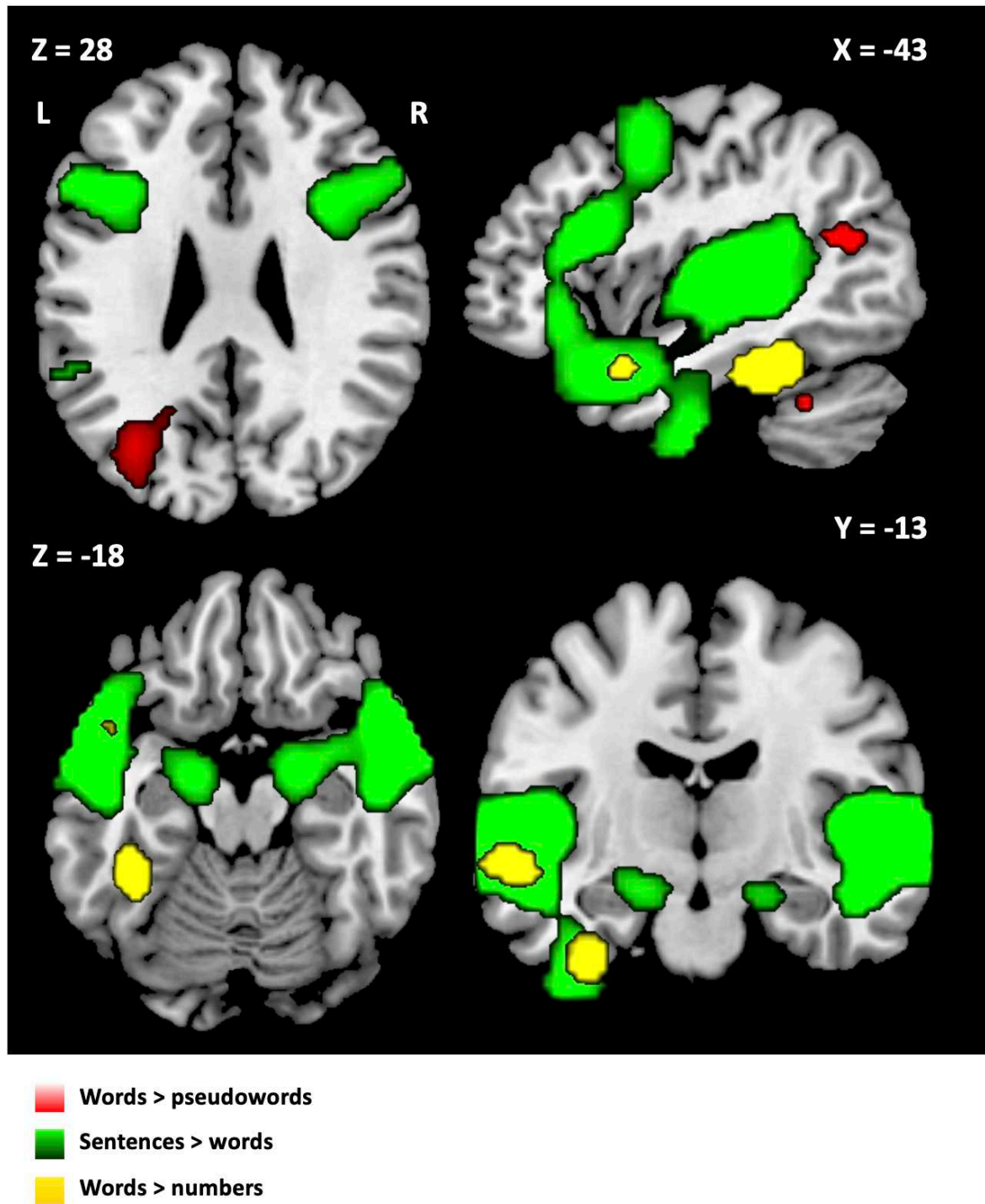
Mean error rates (left column) and response times (right column) for the lexical decision task (Experiment 4) divided according to stimuli lexicity. The first row (A) shows results for words and the second row (B) for pseudowords.

C. Chapter V: Study of neural substrates in functional MRI: comparison of a group of synesthetes and a group of controls

- Supplementary Figure S5.1
- Supplementary Figure S5.2
- Supplementary Figure S5.3
- Supplementary Figure S5.4
- Supplementary Figure S5.5
- Supplementary Table S5.1

Supplementary figure 5.1

Univariate comparison between the 4 speech conditions



In **Experiment 1**, we compared activations induced by the 4 speech conditions (sentences, lists of words, lists of pseudowords, numbers). We computed univariate contrasts of words vs pseudowords, words vs sentences, and words vs numbers, in both directions. Averaging synesthetes and controls, we found:

Appendix:

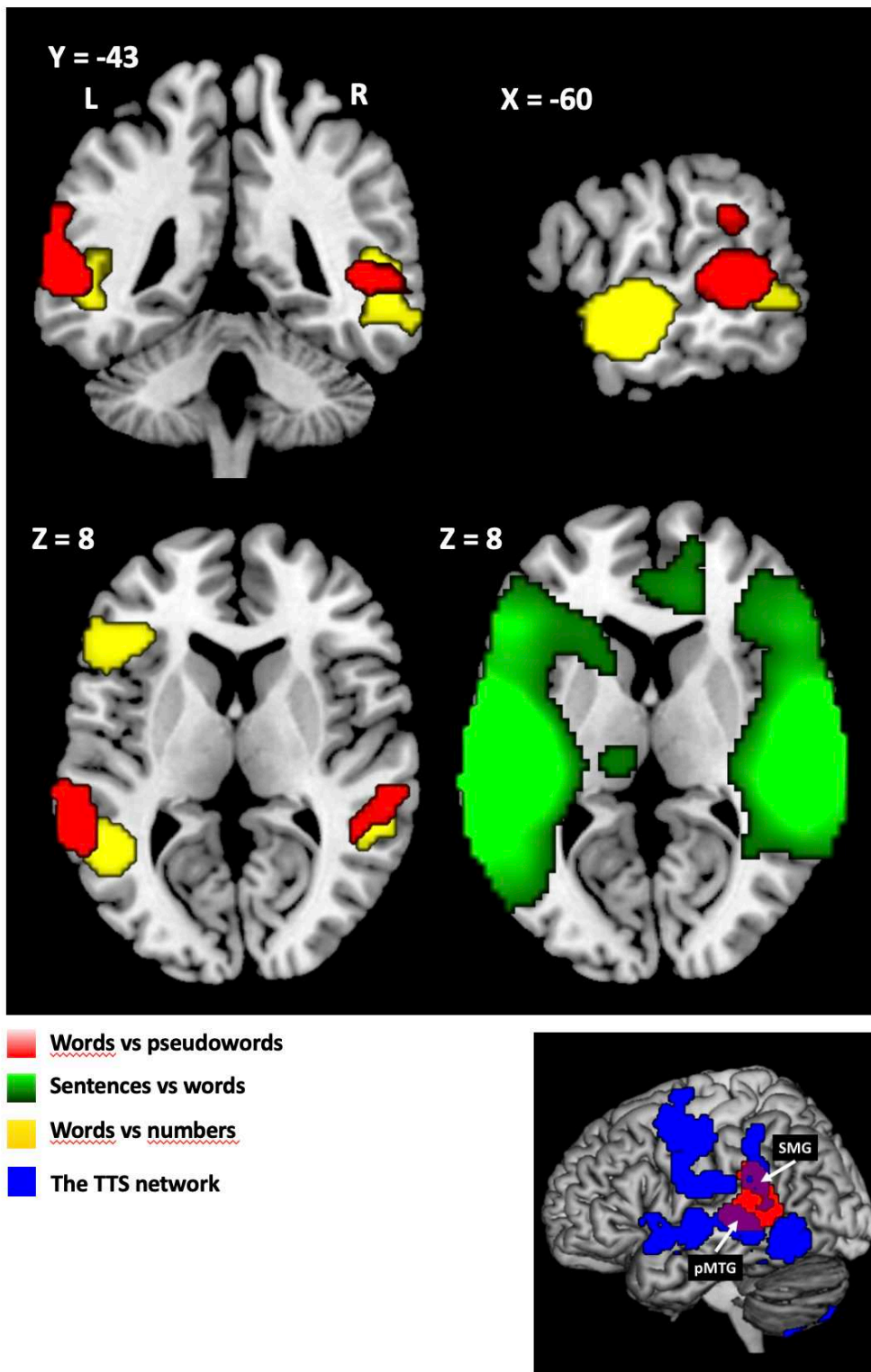
Supplementary material

1. stronger activation by words than pseudowords in the left angular gyrus (MNI -30 -71 33; Z=4.83);
2. stronger activation by sentences than words in an extensive bilateral fronto-temporal network; conversely, there was stronger activation by words than sentences, actually corresponding to stronger deactivation by sentences in the default mode network;
3. stronger activation by words than numbers in the left fusiform gyrus from about y=-50 to -5 (MNI -38 -36 -24; Z=5.04; MNI -32 -8 -37; Z=4.10) and in the left anterior STS/STG (MNI -58 -8 -7; Z=4.92).

None of those contrasts between speech stimuli differed between synesthetes and controls.

Statistical threshold: $p < 0.001$ voxel-wise, and $p < 0.05$ cluster-wise, FWE-corrected for multiple comparisons across the whole brain.

Supplementary figure 5.2
Multivariate decoding between the 4 speech conditions



In **Experiment 1**, we also used an MVPA searchlight to decode activation by words vs each of the other speech conditions. Averaging both groups, we found:

Appendix:

Supplementary material

1. the left posterior superior temporal sulcus (STS) / SMG (MNI -65 -41 6; Z=4.73) and the right STS / anterior STG (MNI 65 -24 -4, Z=4.26) distinguished words from pseudowords;
2. extensive bilateral fronto-parieto-temporal regions (MNI -55 -8 3; Z>8) distinguished words from sentences;
3. the left anterior STG (MNI -55 -8 -4; Z=5.85), the left posterior STS (MNI -48 -54 10; Z=3.94), the right angular gyrus (MNI 45 -64 28, Z=4.36), and the right posterior STS (MNI 55 -41 0, Z=4.24) distinguished words from numbers.

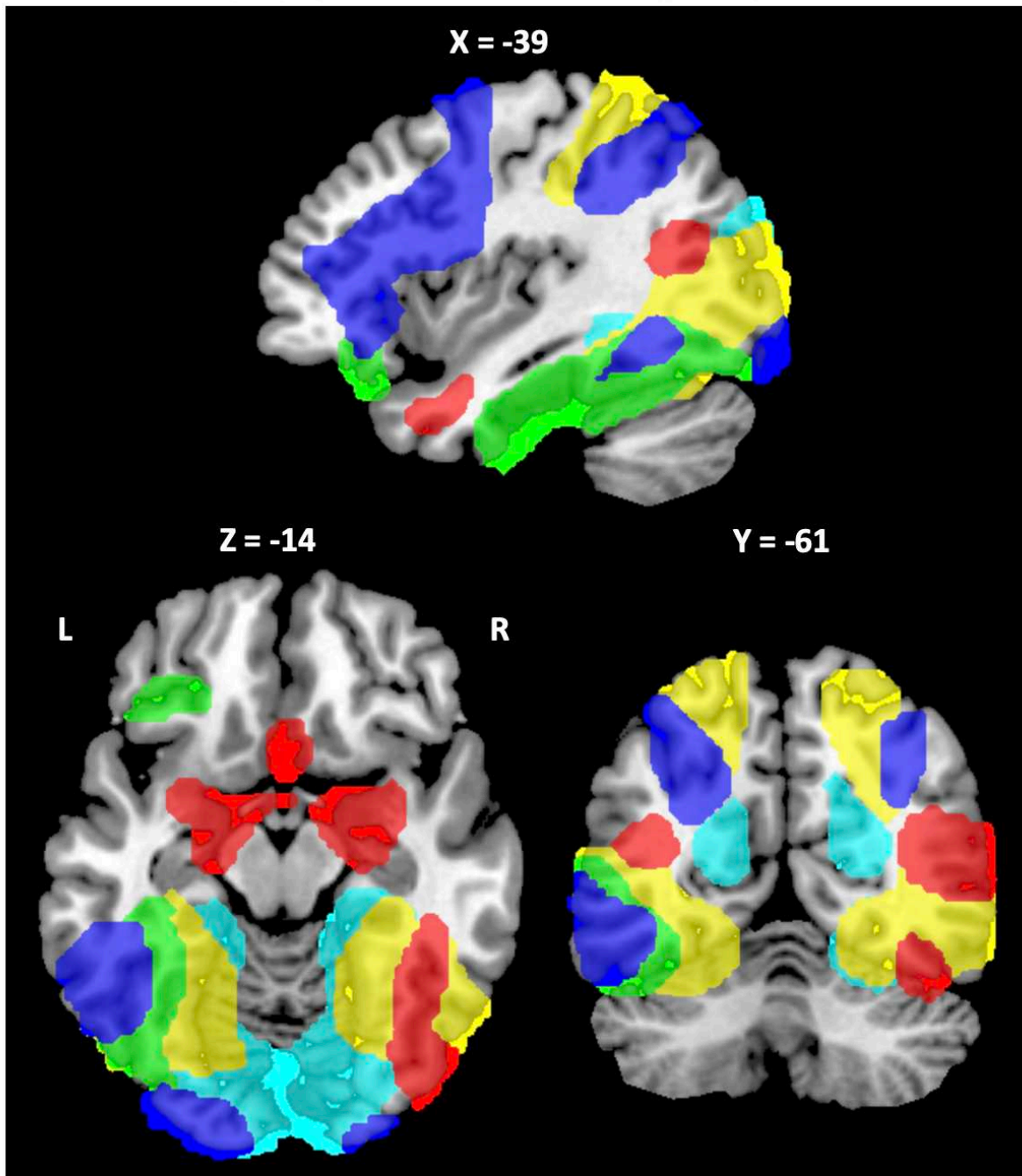
Like in univariate analyses, we found no difference between synesthetes and controls.

Statistical threshold: $p < 0.001$ voxel-wise, and $p < 0.05$ cluster-wise, FWE-corrected for multiple comparisons across the whole brain.

The bottom panel shows the overlap of the left-hemispheric region decoding words from pseudowords (red), and the posterior STG and SMG components of the TTS network (blue).

Supplementary figure 5.3

Category-specific activations in all participants



Activations in synesthetes and controls

- Words > (tools + faces + houses)
- Faces > (words + tools + houses)
- Tools > (words + faces + houses)
- Houses > (words + faces + tools)
- Words > numbers

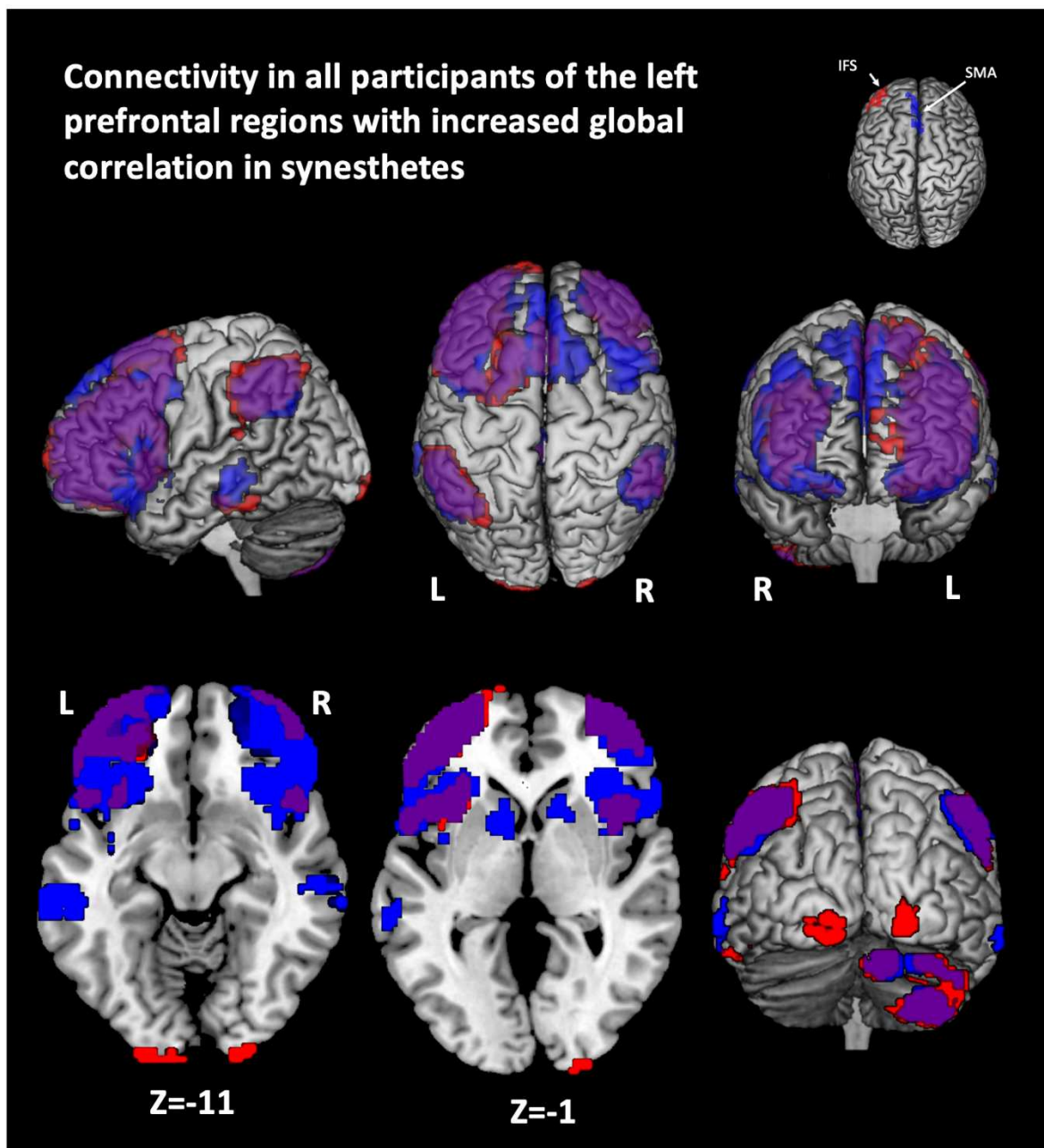
Appendix:

Supplementary material

In **Experiment 2**, we contrasted faces, houses, and tools each minus the other two and words. Averaging both groups, we found the usual VOTc mosaic comprising the bilateral LOC for tools (left: MNI -40 -74 3, $Z>8$; right: MNI 45 -64 -4, $Z>8$) and PPA for houses (left: MNI -25 -48 -7, $Z>8$; right: MNI 28 -46 -7, $Z>8$), and the right-hemispheric FFA (MNI 42 -46 -22, $Z>8$) and OFA (MNI 50 -64 16, $Z>8$) for faces. We also contrasted words vs numbers in both directions. There were stronger activations for words than numbers in the left-hemisphere, along the ventral occipitotemporal cortex from about $y=-90$ to $y=0$, peaking close to the VWFA (MNI -42 -38 -22; $Z=7.63$), the posterior STS (MNI -55 -54 6; $Z=5.71$), and the IFG down to the orbitofrontal cortex (MNI -45 32 10; $Z=6.69$). There were no stronger activations for numbers than for words. None of those contrasts differed between synesthetes and controls.

Statistical threshold: $p<0.001$ voxel-wise, and $p<0.05$ cluster-wise, FWE-corrected for multiple comparisons across the whole brain.

Supplementary figure 5.4



In **Experiment 3**, we looked at the connectivity of the IFS (red) and pre-SMA (blue) during rest. The seeds were identified by virtue of their stronger Global Correlation in synesthetes than in controls. The top right insert shows the location of the seeds. Averaging both groups, those two seeds had similar patterns of bilateral connectivity with the lateral (left: MNI -34 56 12, $Z > 8$; right: MNI 38 58 10, $Z = 7.53$) and mesial (MNI 2 34 40, $Z > 8$) prefrontal cortex and the inferior parietal lobule (left: MNI -50 -54 40, $Z = 7.12$; right: MNI 52 -48 40, $Z = 6.91$), the middle (left: MNI -58 -26 -18, $Z = 5.24$; right: MNI 62 -24 -14, $Z = 4.43$) and inferior temporal gyri for the pre-SMA and IFS seeds respectively, plus the occipital poles for the IFS seed (left:

Appendix:

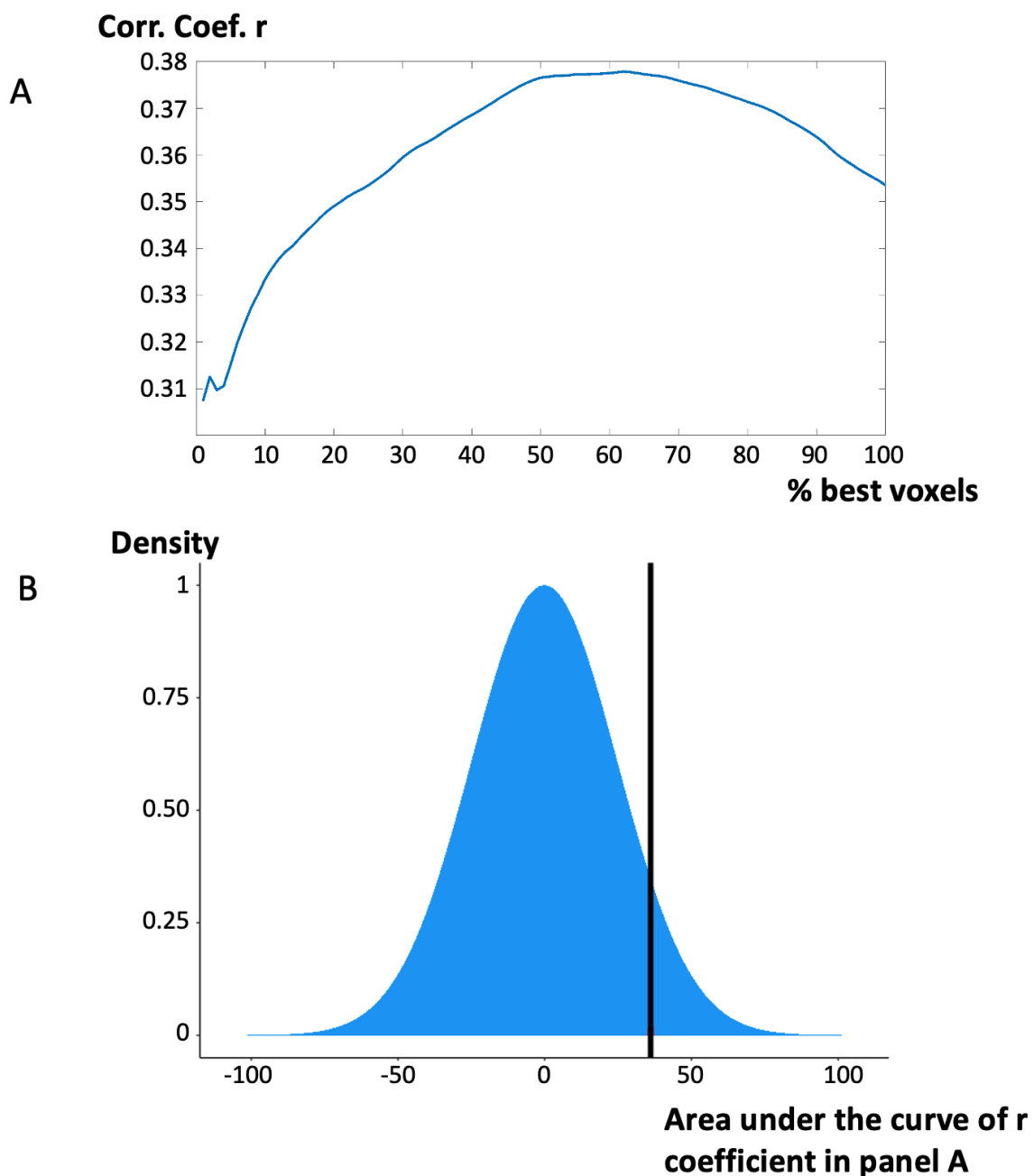
Supplementary material

-12 -104 -14, Z=4.18; right: MNI 22 -104 -2, Z=4.04). For regions showing connectivity with both seeds, the reported coordinates correspond to the connectivity with the pre-SMA.

Statistical threshold: $p < 0.005$ voxel-wise, and $p < 0.05$ cluster-wise, FWE-corrected for multiple comparisons across the whole brain.

Supplementary figure 5.5

Correlation between the number of associated synesthesias and the mean Global Correlation value in a certain % of voxels in the IFS seed.



Experiment 3: In each synesthete, we selected the voxels with the highest Global Correlation from the left IFS region with higher GC in synesthetes than in controls.

(A) We used 100 different thresholds for selecting the voxels (the 1% to 100% best voxels, with a 1% step), and computed at each threshold the correlation between the mean global correlation and the number of associated synesthesia. All R values were positive (all $R > 0.30$), which would be unexpected in the absence of an actual positive correlation.

(B) To statistically assess this observation, we performed 10.000 permutations of the number of synesthesia, and for each permutation computed the equivalent of the curve in panel A, and computed the area under this curve. The plot represents the distribution of the 10000 values of this area. We compared the original area (black vertical line) to the permuted distribution (blue) with a Bayesian Crawford t-test (Crawford and Garthwaite, 2007), and found that it was larger than 93% of the permuted values ($Z=1.47$, $p=0.071$, $95\%CI=0.07-0.08$).

Supplementary table 5.1

MNI coordinates			
X	Y	Z	
-	-46	-	Fusiform gyrus
44.5		18.5	
-46	-47	43	Inferior parietal lobule
-	15.2	8.8	Inferior frontal gyrus
48.8			
-50	-60	-9	Inferior temporal gyrus
-52	-43	21	Post. superior temporal gyrus
-50	-	5	Superior temporal gyrus
	30.5		
-	-	5	Middle temporal gyrus
54.5	51.5		
-	-	34.8	Supramarginal gyrus
49.2	44.4		
-42	4	36	Precentral gyrus
-34	-62	50	Superior parietal lobule

Appendix:

Supplementary material

Mean coordinates of ROIs involved in dyslexia according to 4 meta-analyses combined in Feng et al. (2020).

D. Chapter VI: Increased core-periphery connectivity in tickertape synesthetes.

- Supplementary Table S6.1
- Supplementary Table S6.2
- Supplementary Table S7.3

E. Chapter VII: Study of conscious access to visual perception in a patient with cortical blindness

- Supplementary Table S7.1
- Supplementary Table S7.2
- Supplementary Table S7.3

Methods

Healthy volunteers

Two groups of healthy controls participated in the study. One group (G1) included 22 participants, aged 20-36 years (median 28 years, 10 men). The other group (G2) included 14 older controls, aged 51-75 years (median 64 years, 5 men). All participants were native French speakers, right-handed according to the Edinburgh Inventory [16], had no history of neurological or psychiatric disorders. The research was approved by the institutional review board of the INSERM (protocol C13-41), and participants provided informed written consent.

MRI Brain anatomy

For the patient and for G1, an anatomical T1-weighted image was acquired: TR 2.3 s; TE 2.76 ms; flip angle 9°; voxel size 1 × 1 × 1 mm). For G2, an anatomical T1-weighted image was acquired: TR 2.3 s; TE 4.18 ms; flip angle 9°; voxel size 1 × 1 × 1 mm).

MRI Mask definition

A lesion mask was manually defined with MRIcro (<https://www.nitrc.org/projects/mricro/>), including part of the ventricles' enlargement which resulted of the lesion, and all the white / grey matters with signal abnormalities. A whole brain mask was also manually defined with MRIcro.

MRI Preprocessing

For the patient, we used Clinical Toolbox (<https://www.nitrc.org/projects/clinicaltbx/>), a toolbox used to normalize anatomical images of brain-lesioned patients, to normalize and to estimate deformation fields from native to MNI spaces. For G1 and G2, we segmented and normalized the anatomy to MNI using SPM12 (Wellcome Institute of Imaging Neuroscience, London, UK) implemented in Matlab.

Active visual stimulation fMRI experiment

Stimuli and procedure

The patient was presented with an alternation of blocks of pictures (6 s per block) and periods of rest (4 s per period). Each stimulation block included eight pictures from one of the following categories: printed words, numbers, faces, houses and tools. During the whole experiment, a grey circle embedded in a black background. During stimulation, the stimulus was displayed above this background, and “blank” stimulus consisting of the grey circle on the black background only. Each stimulus was displayed for 400 ms and followed by a 400 ms “blank” stimulus. A black central fixation cross was always present, to minimize eye-movements. The experiment included 15 s of initial rest, followed by 80 blocks of pictures (16 for each category) and a 20 s period of rest every 10 blocks, thus defining a “maxi-block”. Each category was presented twice within a “maxi-block”. Blocks were presented in pseudorandom order to maximize the variety of transitions between conditions while avoiding repetition of the same condition in successive blocks. Healthy participants were exposed to the same visual paradigm while they were asked to press a button with their left thumb whenever an odd consisting of a picture of 5 “#”, which was present in 50% of blocks.

MRI acquisition

Appendix:

Supplementary material

Functional images were acquired on a Siemens 3T MAGNETOM Prisma scanner equipped with a 64-channel receive-only head coil: TR 1660 ms; multi-TE 14.2, 35.39, 56.58 ms; flip angle 74°; voxel size 2.5 × 2.5 × 2.5 mm; 60 slices.

Preprocessing

Using `afni_proc.py`, all echo timeseries were slice-time corrected, motion correction was computed on the first echo and applied to all echos, and echo images were merged using `t2smmap.py` from the `meica.py` toolbox provided with AFNI: <http://afni.nimh.nih.gov/afni/>. Then, using SPM12, functional time-series were co-registered to the anatomical volume, and spatially smoothed (6 mm FWHM).

Statistical analysis

All statistics were performed within native space. We used a general linear model (GLM) with multiples regressors, including 24 motion parameters, cardiac and respiratory regressors, as their (cardiac x respiratory) regressor, noise from nuisance ROI (white matter or cerebrospinal fluid) and outlier volumes resulting from TAPAS toolbox (<https://github.com/translationalneuromodeling/tapas>), whose purpose is the physiological noise correction of fMRI data using peripheral measures of respiration and cardiac, as well as a high-pass filter (128 s cutoff). 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: one regressor for each of the 5 categories of stimuli, plus a regressor for basal condition (=rest) and one for responses to targets. We set the first-level voxel-wise cluster-forming threshold to $p < 0.001$, and the cluster-wise threshold to $p < 0.05$ corrected for multiple comparisons across the whole brain or within ROIs. Whole-brain analyses were performed within the manually drawn whole-brain mask.

Masks definition

In addition to the whole-brain approach, we also restricted the analyses to a mask of the primary visual cortex. We manually defined the mask with MRICro, respecting the lesion and ventricles. The mask was then smoothed (6 mm FWHM), and included 28973 voxels.

Resting state fMRI experiment

Acquisition

*Appendix:
Supplementary material*

The patient and controls from G1 and G2 had a resting state acquisition. Multi-echo (ME) fMRI sequences were used for resting-state for the patient and G1 individuals. Single-echo (SE) sequences were used for resting-state for G2 individuals.

Resting state parameters

For the patient, functional MRI scans (TR/multi-TE/flip angle = 1660 ms / 14.2, 35.39, 56.58 ms / 74°, voxel size = 2.5 × 2.5 × 2.5 mm, 60 slices) were acquired on a Siemens 3T MAGNETOM Prisma scanner equipped with a 64-channel receive- only head coil.

For G1, functional MRI scans (TR/multi-TE/flip angle = 1300 ms / 15, 34.24, 53.48 ms / 68°, voxel size = 3 × 3 × 3 mm, 48 slices) were acquired on a Siemens 3T MAGNETOM Prisma scanner equipped with a 64-channel receive- only head coil.

For G2, functional MRI scans (TR/TE/flip angle = 2580 ms / 30 ms / 90°, voxel size = 3 × 3 × 3 mm, 40 slices) were acquired on a Siemens 3T MAGNETOM Verio scanner equipped with a 64-channel receive- only head coil.

Procedure

During the resting state acquisition, young controls had their eyes closed, whilst the patient kept his eyes open because of motor impersistence, and was asked to maintain fixation in front of him at a white cross on a black screen that he could not consciously perceive, and older controls had their eyes open, staring at a black screen. The room was in the dark.

Preprocessing

For G1 and for the patient, using `afni_proc.py`, all echo timeseries were slice-time corrected, motion correction was computed on the first echo and applied to all echos, and echo images were merged using `t2smmap.py` from the `meica.py` toolbox.

For G2, using SPM12, we applied slice-timing correction and motion correction.

Then, to avoid finding low frequency correlations in subjects with longer scanning time, we shortened the number of volumes in G1 from 400 to 344 and in the patient from 360 to 270 volumes, in order to reach the same duration of approximately 7 min 26 secs for all subjects.

Then, for all groups, using SPM12, functional time-series were co-registered to the anatomical volume, normalized to MNI space (using deformation field parameters resulting from Clinical

Appendix:

Supplementary material

toolbox for the tested patient), and resampled to 3 mm cubic voxels when needed (for all subjects having the same resolution) and spatially smoothed (6 mm FWHM).

Finally, using conn-toolbox (version v.18.b <http://www.nitrc.org/projects/conn>), a linear detrending and a band-pass filter of 0.008–0.09 Hz was applied.

Statistical analysis

All statistics were performed within MNI space. Tapas toolbox was not used, since controls were scanned during a relatively older protocol, in which no physiological variable were recorded, hence we applied the same preprocessing to all subjects, and we only used the 6 movement regressors from motion correction. Age was added as a covariate, since the age of the two control groups was clearly different.

Using conn-toolbox, we conducted seed-based functional connectivity analyses at first- and at second-level. The primary visual cortex smoothed mask, as defined above, was used as a seed. All results were corrected for multiple comparison using SPM's default FWE-cluster correction with a voxel-level $p < 0.001$ (uncorrected) and cluster-level $p = 0.05$, except when specified otherwise.

Masks definition

We finally defined a visual cortex mask, using the brainnetome atlas (<https://atlas.brainnetome.org/>), and including the bilateral caudal cuneus gyri, occipital polar cortices, medial superior occipital gyri, ventro-medial parieto-occipital sulci, dorso-medial parieto-occipital sulci, rostral lingual gyri, rostral cuneus gyri, caudal lingual gyrus and inferior occipital gyri. All these regions were at least partially included in the visual cortex mask of M.G and were so included in this mask.

Results

Detailed medical case-report:

A 59 y.o. male patient was hospitalized in March 2020 in ICU for an acute respiratory distress syndrome secondary to SARS-Cov2 infection. Mechanic ventilation was required for 35 days, including four sessions of prone positioning. During his stay in ICU several notable complications occurred including: (i) a septic shock related to Haemophilus Influenza lung infection, (ii) a severe skin rash with hypereosinophilia (>1.4 G/L) and systemic syndrome

*Appendix:
Supplementary material*

without identified cause, (iii) an acute renal failure (KDIGO 3) with renal replacement therapy (i.e.: hemodialysis and hemofiltration) for several weeks, (iv) spontaneous right hemopneumothorax requiring surgical treatment, and (v) a severe posterior encephalopathy syndrome with refractory status epilepticus (RSE). This dramatic neurological complication is the causal event of the current neurological syndrome that motivated the present study. The etiology of this non-reversible posterior encephalopathy is not univocal and may originate from sequellae of the initial RSE but also from SARS-Cov2 brain infection or inflammation, from non-specific encephalopathy related to the documented events including: septic shock, hypoxemia and sustained metabolic encephalopathy. Note that these different possible causes are not mutually exclusive, and that sequellae of RSE were retained as the most probable cause possibly complicated by some of the other factors we listed here.

Table S7.1

Task category	Sub-Task	Score
Digit spans	Digit span direct	3
	Digit span reverse	impossible
Frontal Assessment Battery	Go - No Go	0/3
	Conflicting instructions	0/3
	Similarities	1/3
	Lexical Fluency	1/3
Verbal series recitation	Counting (1-10) direct	10/10
	Counting (1-10) reverse	impossible
	Days of the week direct	7/7
	Days of the week reverse	impossible
Aphasia Rapid Test (ART)		4/24 (normal score = 0/24)
Self body-parts designation	(with L/R instructions)	12/12
Space-Time orientation	Space	2/5
	Time	2/5

Table S7.1: Neuropsychological examination of non-visual abilities

Table S7.2

	Task	Correct Response

Appendix:
Supplementary material

Ventral pathway tasks	word reading	Impossible
	letter reading	Impossible
	digit reading (0 to 9)	Impossible
	color naming	Impossible
	object naming	Impossible
	object discrimination	Impossible
Dorsal pathway tasks	fixation	Impossible
	saccade	Impossible
	orienting	Impossible
	pointing	Impossible
	grasping	Impossible

Table S7.2: Behavioral performance on ventral and dorsal visual tasks

Additional fMRI results:

Given that the two control groups G1 and G2 were scanned on different magnets, and G1 controls were younger than the patient, we performed additional analyses to confirm our findings. In order to make sure that the overall differences which we observed between the patient and controls were not due to age or to scanner differences, we compared separately the patient to G1 and G2 groups, and found that the main differences were remarkably replicated across both analyses, using the same statistical thresholds as in the global comparison.

The G1 > Patient comparison showed higher functional connectivity of the visual cortex seed with the left medial orbitofrontal cortices, the left anterior prefrontal cortex (MNI -32 58 4, $Z=4.88$), the right temporal pole, the bilateral dorsal anterior cingulate cortices, and the bilateral posterior cingulate cortex. The G2 > MG comparison showed higher functional connectivity of the visual cortex seed with the left medial orbitofrontal cortex, the left anterior prefrontal cortex (MNI -36 58 4, $Z=4.26$), the right temporal pole, the bilateral dorsal anterior cingulate cortices, the left anterior prefrontal cortex, the left temporal pole, the right pars orbitalis, the right lateral orbitofrontal cortex and the left front eye fields (see Supplementary Table S6.2 below).

Finally, we compared functional connectivity between patient's visual cortex and healthy controls visual cortex, because by restraining our comparison to the patient's visual cortex mask we miss voxels from healthy volunteers visual cortices. Setting the voxel-wise cluster-forming threshold to $p<0.005$, and the cluster-wise threshold to $p<0.05$, we found the same clusters in the right temporal pole (MNI 30 16 -44, $Z=4.98$) and the left anterior prefrontal cortex (MNI -

38 62 8, $Z=3.97$, which was absent with a 0.001 voxel-wise threshold), but also in the left posterior cingulate cortex (MNI 10 -52 28, $Z=3.80$), the left temporal pole (MNI -18 -8 -40, $Z=4.90$), medial orbitofrontal cortices (MNI -2 20 -26, $Z=4.37$), the right parahippocampal cortex (MNI 28 -22 -32, $Z=4.18$) and in the right prefrontal cortex (MNI 20 70 -8, $Z=4.15$).

Table S7.3

Region (left hemisphere)	Contrast	Peak coordinates (MNI)	Z value	Cluster size	p-value (cluster-level, FWE corrected)
Left medial orbitofrontal cortex	G1 > Patient	-2 20 -26	5.14	211	0.01 *
	G2 > Patient	-8 10 -16	4.40	441	<0.001 *
Left anterior prefrontal cortex	G1 > Patient	-32 58 4	4.88	485	<0.001 *
	G2 > Patient	-36 58 4	4.26	461	<0.001 *
Right temporal pole	G1 > Patient	16 4 -48	4.84	637	<0.001 *
	G2 > Patient	24 -2 -46	4.89	692	<0.001 *
Bilateral dorsal anterior cingulate cortices	G1 > Patient	-6 46 14	4.24	219	0.008 *
	G2 > Patient	6 58 2	4.06	256	<0.001 *
Bilateral posterior cingulate cortex	G1 > Patient	-6 -22 38	3.8	200	0.013 *
	G2 > Patient	NA	NA	NA	NA
Left anterior prefrontal cortex	G1 > Patient	NA	NA	NA	NA
	G2 > Patient	18 64 -10	4.37	116	0.014 *
Left temporal pole	G1 > Patient	NA	NA	NA	NA
	G2 > Patient	-14 -4 -40	4.35	143	0.004 *
Right pars orbitalis	G1 > Patient	NA	NA	NA	NA
	G2 > Patient	40 26 -16	4.35	146	0.004 *
Right lateral orbitofrontal cortex	G1 > Patient	NA	NA	NA	NA
	G2 > Patient	28 10 -14	4.08	91	0.045 *

Appendix:

Supplementary material

Left front eyefields	G1 > Patient	NA	NA	NA	NA
	G2 > Patient	-38 16 56	3.78	101	0.028 *

* Significant cluster-level P, with voxelwise $P < 0.001$ and clusterwise $P < 0.05$ corrected for multiple comparisons across the whole brain

Table S7.3: Resting-state functional connectivity with visual cortex larger in G1 and G2 groups than in the patient

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