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Intégration et topographie fonctionnelles : l'influence de la cécité précoce.

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Résumé

L'organisation fonctionnelle du cerveau humain montre une similarité interindividuelle remarquable et robuste, suggérant que sa structure fonctionnelle est innée. Cependant, cette observation n'est pas sans équivoques, le cerveau est aussi plastique : son organisation peut être influencée par des événements survenant tôt dans la vie. Parmi les plus marquants, on retrouve la perte de vision précoce ou congénitale. En effet, il a été démontré à plusieurs reprises que, chez les personnes non-voyantes, les régions habituellement dédiées à la vision (ex. : lobes occipitaux) se réorganisent afin d'analyser des stimuli auditifs et tactiles.

Les plus récentes études chez les non-voyants se sont intéressées à la relation entre la réorganisation des lobes occipitaux et les deux principes organisateurs fondamentaux du cerveau : la localisation fonctionnelle et l'intégration fonctionnelle. Le premier signifie que des fonctions spécifiques mobilisent des régions circonscrites du cerveau, tandis que le second signifie que les régions du cerveau communiquent entre elles afin de créer un tout cohérent. Toutefois, l'ampleur de l'effet de la cécité sur l'organisation du cerveau est encore inconnue. Premièrement, la topographie de modules possédant une fonction spécifique n'a encore jamais fait l'objet d'un examen direct, approfondi et holistique chez les non-voyants, et ce, malgré le fait qu'il s'agisse d'une caractéristique clef de la localisation fonctionnelle. En outre, les études examinant l'intégration fonctionnelle chez les non-voyants semblent en contradiction avec celles qui l'étudient de manière indirecte. Cette dépendance des résultats sur la méthode employée nécessite une étude approfondie des éléments influençant ces résultats afin que des conclusions appropriées puissent être tirées.

Ainsi, bien que la plasticité cérébrale chez les personnes non-voyantes fasse l'objet de plusieurs études, son influence sur l'organisation fonctionnelle du cerveau reste à approfondir

et est sujette à débats. De ces faits, l'objectif principal de la présente thèse est d'examiner l'influence de la cécité précoce sur la topographie des modules fonctionnels ainsi que sur l'intégration fonctionnelle. Pour cela, trois expériences distinctes ont été conduites.

La première expérience a été élaborée afin de comparer la disposition spatiale des modules fonctionnels des voyants à celle des non-voyants. À cette fin, une méthode a été développée qui permettait d'examiner la question de manière holistique et sans biais à partir de données d'imagerie par résonance magnétique. Les résultats indiquent que seules les régions « visuelles » de bas niveau, les pôles occipitaux, sont sous-divisées de manière différente chez les personnes non-voyantes. À l'opposé, les régions de haut niveau maintiennent leur disposition spatiale. Ceci suggère que l'établissement de modules fonctionnels au sein du lobe occipital dépend à la fois d'entrées sensorielles visuelles, ainsi que du niveau hiérarchique de la région.

La seconde expérience de cette thèse visait à examiner certains facteurs qui pourraient causer les contradictions observées par les études sur l'intégration fonctionnelle chez les non-voyants. Les données d'une des méthodes employées pour mesurer l'intégration fonctionnelle, l'état de repos mesuré par imagerie par résonance magnétique fonctionnelle, ont été comparées à celles obtenues lorsque les participants se concentraient sur une tâche auditive. D'abord, les résultats démontrent une dépendance de l'intégration fonctionnelle sur l'état cognitif des participants, suggérant que les différences entre non-voyants et voyants observées jusqu'ici doivent être interprétées prudemment. De plus, et d'une importance inédite, les résultats démontrent que les pôles occipitaux possèdent des caractéristiques fonctionnelles différentes chez les non-voyants que chez les voyants. Ces caractéristiques suggèrent que les pôles sont impliqués dans un nombre plus important de réseaux chez les personnes non-voyantes.

La troisième expérience de cette thèse a été conçue pour faire suite aux résultats des deux premières. Spécifiquement, elle valide une méthode qui sera employée afin d'examiner des régions qui, selon les deux premières expériences de cette thèse, possédaient des caractéristiques fonctionnelles réorganisées chez les personnes non-voyantes : les pôles occipitaux. Cette méthode, développée afin de contrôler la difficulté d'une tâche de perception de voix humaines, s'est avérée valide. Ainsi, elle pourra être employée lors d'études futures afin de désambiguïser la fonction des pôles occipitaux chez les non-voyants. De plus, les résultats de l'expérience révèlent plusieurs mécanismes d'action sous-jacents la perception de voix chez l'être humain.

Globalement, les deux premières expériences constituant cette thèse mettent en évidence les caractéristiques fonctionnelles réorganisées au sein des pôles occipitaux chez les PNV, une région encore sous-étudiée chez cette population. La troisième étude présente une méthode permettant d'étudier ce phénomène. Les caractéristiques dévoilées par ces expériences pavent la voie vers de nouvelles hypothèses et études qui permettront d'approfondir notre conception du cerveau et de la plasticité cérébrale.

Mots-clefs : Cécité précoce, plasticité cérébrale, connectivité fonctionnelle, topographie fonctionnelle, imagerie cérébrale.

Abstract

The brain's functional organization shows a remarkable similarity across individuals suggesting that its functional structure is innate. However, this observation is not unequivocal for the brain is also plastic; its organization is subject to changes following important early life experiences. Of such event, early or congenital vision-loss features among the most outstanding. Following blindness, cerebral regions usually involved with visual analysis (e.g. occipital lobes) are reorganized to process auditory, tactile, and olfactory stimuli, as well as higher order cognitive tasks such as memory and language.

Recent studies on blind individuals have focused on the relationship between the reorganization of the occipital lobes and the fundamental organizational principles of the brain: functional localization and integration. The first indicates that specific functions take place within circumscribed cerebral regions, whereas the second indicates that these regions communicate together. However, the extent to which blindness influences the brain's organization is still unknown. First, the topography of modules possessing specific functions has yet to be the object of a direct, in depth, and holistic investigation in blind people. This is true even though module topography is a key characteristic of spatially localized functions. Moreover, studies investigating functional integration in blind individuals appear to contradict those which study integration indirectly. The dependence of results upon the method employed demands further investigation of the elements that might influence integration so that appropriate conclusions can be drawn.

Thus, even though blindness-induced brain plasticity has been the object of multiple studies, its influence upon cerebral organization is partly subject to debate, and must be further defined. Accordingly, the main objective of this thesis was to study the influence of early

blindness upon the topography of functional modules and upon functional integration. In order to do so, three distinct experiments were carried.

The first experiment was conceived so as to compare the spatial topographies of functional modules across blind and sighted participants. To this end, a holistic and bias-free method, which made use of resting-state functional magnetic resonance imagery, was developed. Results indicate that only blind people's occipital poles possess modules which were topographically different from those found in sighted individuals whereas higher level "visual" areas do not show this effect. This suggests that the formation of functional modules within the "visual" cortices depends on both sensory inputs as well as the hierarchical level of a region.

The second experiment of this thesis examined factors which might cause the contradictions observed by studies on blind people's functional integration. Data obtained from a method devised to measure functional integration, resting-state functional magnetic resonance imagery, were compared to those obtained while participant focused on auditory stimuli. Results are twofold. First, results showed that group differences in functional integration vary as a function of the participant's cognitive states, suggesting that differences in functional integration observed using resting-state fMRI should be interpreted with caution. Second, our results reveal novel findings pertaining to the occipital poles of blind people; these regions showed strikingly different characteristic following early visual loss which are suggestive of their role in a multitude of networks.

The third experiment of this thesis was designed following the first two. Specifically, it validates a method to examine the functions of blind people's occipital poles, a region which had been shown to possess reorganized functional characteristics by the first two experiments of this thesis. A new methodology was designed to control the difficulty of a voice

discrimination task, showing its validity. Thus, it will be possible to use it in future studies to investigate the function of the occipital lobes in blind people. Furthermore, results from the experiment revealed multiple mechanisms which might underlie voice perception in humans.

Overall, the experiments forming this thesis evidence a reorganisation of the occipital poles' functional characteristics in early-blind individuals. Additionally, they provide methods needed to investigate the functions of this understudied region. Most importantly, the observation that blind people's occipital poles show modified functional characteristics paves the way to new hypotheses and studies which will allow to further investigate and deepen our understanding of the human brain and its plasticity.

Key words: Early blindness, cerebral plasticity, functional connectivity, functional topography, functional imaging.

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Liste des sigles et abréviations

CF : connectivité fonctionnelle

ER : état de repos

IRMf : imagerie par résonance magnétique fonctionnelle

MDS : multiple demand system; système répondant à des demandes multiples

PNV : personnes non-voyantes

PV : personnes voyantes

TEP : tomographie par émission de positrons

SMT : stimulation magnétique transcrânienne

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Introduction générale

Préambule

La vision moderne de la pensée humaine et du fonctionnement du cerveau est fondée non pas sur l'étude de cerveaux sains, mais bien sur l'observation de cerveaux ayant subi une lésion (chez l'humain : Bouillaud, 1825; chez divers animaux : Flourens, 1842). Cette méthodologie s'inspire du concept selon laquelle l'élimination de facteurs clefs d'un processus, ici une partie circonscrite du cerveau, aura nécessairement un impact sur l'exécution de ce même processus, ici un comportement ou un mécanisme cognitif ou perceptuel. Un célèbre exemple d'une des premières applications de cette méthode au champ de la neuropsychologie nous est fourni par Paul Broca, qui démontra un lien entre une lésion localisée du lobe frontal et l'aphasie (perte de la production du langage; Broca, 1861).

Encore pertinente aujourd'hui (Rorden & Karnath, 2004; Malhotra & Russel, 2015), cette méthode permet non seulement d'étudier le rôle de différentes régions du cerveau, mais aussi d'autres facteurs qui influencent les fonctions cérébrales (ex. la cognition et la perception). Parmi ces facteurs, nommons le rôle des sens sur la maturation du cerveau, un phénomène d'une importance capitale pour la présente thèse. Spécifiquement, l'étude des répercussions de la privation sensorielle chez un individu peut nous éclairer sur le rôle qu'a un sens sur le développement des fonctions cérébrales. Considérant que, chez l'humain, près du tiers du cerveau contribue, d'une manière ou d'une autre, au traitement visuel, cela fait de la cécité la privation sensorielle de prédilection pour examiner l'effet qu'ont les sens sur la maturation du système nerveux.

Comme la recension des écrits suivant ce préambule le démontrera, l'étude des effets de la cécité précoce ou congénitale sur le cerveau a connu une popularité grandissante durant les 20 dernières années, apportant d'importantes découvertes au champ de la neuropsychologie,

mais laissant aussi entrevoir un nombre important de nouvelles avenues. Ces études ont non seulement appuyé l'idée populaire selon laquelle la perte d'un sens mène à une compensation de la part des autres sens, elles ont aussi dévoilé que, chez l'aveugle précoce ou congénital, le lobe occipital, responsable de la vision chez les personnes voyantes (PV), acquerrait de nouvelles fonctions liées à l'audition et au tact. Depuis, les études récentes visent à caractériser et cartographier les fonctions du lobe occipital des aveugles ainsi que la communication qui existe entre les différentes régions cérébrales. Est-ce que la topographie de ces régions et leur communication dépend de la vision ou est-il inné? Ces caractéristiques sont-elles modifiées suite à une cécité précoce ou congénitale? Voici les questions abordées par les études actuelles sur la privation visuelle et le développement du cerveau.

Court survol historique

L'impact de la cécité sur la pensée humaine est un sujet qui a enflammé les débats philosophiques et scientifiques dès l'avènement du Siècle des lumières. Cet intérêt semble provenir d'une question posée à l'éminent John Locke par le philosophe William Molyneux :

« A Man being born blind, and having a Globe and a Cube, nigh of the same bigness, Committed into his Hands, and being taught or Told, which is Called the Globe, and which the Cube, so as easily to distinguish them by his Touch or Feeling; Then both being taken from Him, and Laid on a Table, Let us Suppose his Sight Restored to Him; Whether he could, by his sight, and before he touch them, know which is the Globe and which the Cube? Or Whether he could know by his sight, before he stretched out his Hand, whether he could not Reach them, tho they were Removed 20 or 1000 feet from Him?» (copie littérale de Molyneux, 1688, p. 483-484)

Cette question sur la nature du savoir humain, communément appelée le problème de Molyneux, a mobilisé l'esprit d'éminents penseurs tels Leibniz, Berkeley et James. Certains étaient de l'opinion que le savoir était transférable d'un sens à l'autre, d'autres étaient de l'avis de Locke et Molyneux selon qui l'adéquation entre deux sens ne pouvait être atteinte qu'avec l'expérience. Il a fallu attendre le début du XXI^e siècle pour que le débat semble arriver à terme : les données récentes, provenant d'individus chez qui on a réséquer des cataractes congénitales, supportent l'idée qu'un apprentissage est nécessaire à la reconnaissance visuelle (Held et al., 2011).

Loin de ne pouvoir nous éclairer que sur la nature du savoir humain, l'étude des impacts de la cécité précoce ou congénitale sur la cognition et la perception humaine peut aussi nous informer sur la flexibilité des limites sensorielles. En effet, 15 ans après que le Dr. Cheselden ait réséqué les cataractes d'un aveugle congénital, Diderot, dans sa « Lettre sur les aveugles à l'usage de ceux qui voyent » (1749), rapporta de manière anecdotique des habiletés sensorielles hors-normes chez des personnes non-voyantes (PNV). Parmi ces dernières, on retrouve une perception des détails auditifs et tactiles plus marquée. Ces anecdotes semblent avoir inspiré une pléthore d'études et de théories (voir Supa, Cotsin, & Dallenbach, 1944, pour une revue historique de la littérature) entre le XVIIIe siècle et le début du XXe siècle. Chacune d'elles visant à trouver et expliquer la source de ces suprahabilités. Parmi les théories découlant de ces études, on retrouve celle de la compensation sensorielle selon laquelle la perte d'un sens mène à une compensation par les autres sens. Autrement dit, la perte de vision entraînerait une superacuité de l'ouïe et du toucher. Cette théorie se basait alors sur l'idée selon laquelle le cerveau possède une force nerveuse (nervous power) distribuée entre les différents sens et que, lorsqu'un sens est manquant, cette force est redistribuée aux sens subsistants. Toutefois, elle a été mise en doute, car l'existence d'une force nerveuse n'était appuyée par aucune étude scientifique (Hayes, 1934). Par contre, si l'existence d'une force nerveuse a été réfutée, cela n'exclut pas que certains PNV puissent compenser leur cécité à l'aide de leurs sens restant.

Compensation sensorielle

Les PNV possèdent-elles réellement et systématiquement des sens plus aiguisés? Si oui, et comme l'existence d'une force nerveuse est un construit sans base, quelles pourraient être les sources de la compensation sensorielle? Ces deux questions sont à l'origine d'un nombre

important d'études examinant l'effet de la cécité sur la perception et le cerveau. La première étape pour y répondre est d'investiguer l'existence systématique et non pas anecdotique des suprahabilités sensorielles des PNV. Pour ce faire, une revue exhaustive des articles étudiant les habiletés tactiles, olfactives et auditives des PNV sera présentée dans cette section.

Un bref survol de ces études montre que le sujet de la superacuité sensorielle des PNV a longtemps été disputé. Toutefois, un consensus s'est lentement formé et supporte la présence d'une compensation sensorielle influencée par plusieurs facteurs. Ensemble, les études présentées ci-dessous soulignent ces facteurs et prouvent l'existence de la compensation sensorielle.

Le tact

L'étude du tact chez les PNV semble, à première vue, ne donner aucune preuve concluante d'une superacuité au niveau de ce sens (Seashore & Ling 1918; Brown & Stratton, 1925); plusieurs études ne montrent aucune différence perceptuelle entre les PNV et les PV (Pascual-Leone & Torres, 1993; Stevens, Foulke & Patterson, 1996; Grant, Thiagarajah, & Sathian 2000; Alary et al., 2009) tandis que d'autres montrent la présence d'une différence statistiquement significative (Grant et al., 2000; Legge, Madison, Vaughn, Cheong, & Miller, 2008; Goldreich & Kanics, 2003;2006; van Boven, Hamilton, Kauffman, Keenan, & Pascual-Leone, 2000; Norman & Bartholomew, 2011; Wong, Gnanakumaran, & Goldreich, 2011). La cause de cette variabilité parmi les résultats a été attribuée parfois à un mauvais appariement des groupes au niveau de l'âge et du sexe et parfois à des différences méthodologiques telle la tâche effectuée par les participants (Voss, 2009). Considérant que des facteurs comme le sexe et l'âge influencent l'acuité tactile (Stevens et al., 1996; Goldreich & Kanics, 2006), un mauvais

appariement au niveau de ces variables pourrait diminuer la significativité statistique des différences observées entre les PV et PNV. En outre, certaines études montrent que l'avantage tactile des PNV dépend de la tâche sur laquelle ils sont testés (Stevens et al., 1996; Grant et al., 2000). Ainsi, afin de clarifier le problème, il est nécessaire de séparer les résultats de différentes tâches et de noter l'importance de la différence entre les groupes (est-elle statistiquement significative? y a-t-il une tendance ou les PNV présentent-ils de moins bonnes performances que les PV).

Lors de tâches d'acuité tactiles passives, durant lesquelles un stimulus (un dôme présentant des sillons ou deux pointes d'un compas) est appliqué aux doigts d'un participant, les PNV performant mieux que les PV, ces différences sont statistiquement significative pour cinq études (Goldreich & Kanics, 2003;2006; van Boven et al., 2000; Norman & Bartholomew, 2011; Wong et al, 2011) et présentent une tendance non significative pour deux (Stevens et al., 1996; Alary et al., 2009). Une seule étude démontrait une moins grande acuité chez les PNV (Grant et al., 2000). De plus, la présence d'une corrélation entre le nombre d'heures de lecture hebdomadaire de Braille et l'acuité suggère que la superacuité des PNV résulte d'un effet de pratique.

En ce qui a trait aux tâches d'acuités actives, durant lesquelles les participants inspectent les stimuli librement (p.ex. stimuli similaires au braille ou braille), elles mettent en évidence un avantage statistiquement significatif chez les PNV (Grant et al., 2000; Legge et al., 2008). D'une manière similaire, les études s'intéressant à la perception de vibrations montrent soit une tendance vers une plus grande acuité chez les PNV (Alary et al., 2009) ou des différences statistiquement significatives allant aussi dans cette direction (Wan, Wood, Reutens, & Wilson, 2010a).

En résumé, les PNV montrent une meilleure acuité tactile que les PV. Quoique cet effet n'apparaisse pas comme statistiquement significatif dans chacune des études, il y est néanmoins présent. Ainsi, il y a une tendance claire vers une compensation sensorielle du tact chez les PNV qui semble relever d'un effet de pratique fortement lié au degré d'expertise en lecture du Braille. Ceci suggère que les suprahabilités des PNV se développent de manière à cibler des comportements précis et utiles à l'utilisateur.

Sens chimiques : L'olfaction et la gustation

Les sens chimiques ont tous deux été investigués chez les PNV. Similairement à l'étude du tact, la recherche sur l'olfaction des PNV a été le sujet de plusieurs débats pour lesquels un consensus n'est apparu que durant la dernière décennie. Il semble que les six études publiées sur le sujet de 1880 à 1980 n'aient que sporadiquement révélé une superacuité olfactive chez les PNV. L'auteur de cette thèse ne peut pas faire une analyse détaillée de ces six études, car elles n'ont été publiées qu'en Allemand et en Italien. Toutefois, Smith, Doty, Burlingam et McKeown (1993), dans une revue de la littérature, rapportent que seulement deux de ces études mettent en évidence de meilleures capacités olfactives chez les PNV. Par contre, la méthode employée par ces études est jugée comme biaisée, car les stimuli sont délivrés avec une bouffée d'air qui peut être détectée même si elle ne contient aucune odeur. De plus, comme pour les études sur le tact, les différences d'acuité olfactives entre les PNV et les PV peuvent être modérées et n'apparaître significatives que dans certaines études, suggérant qu'il faut prendre en compte l'importance de ces différences aussi bien que leur signifiante statistique.

Les études réalisées sur le sujet durant les 20 dernières années montrent une tendance claire vers une perception olfactive supérieure chez les PNV congénitaux. Celle-ci est

particulièrement évidente lorsque les participants doivent nommer une odeur sans qu'on leur donne d'indices (Wakefield, Homewood, & Taylor, 2004; Cuevas, Plaza, Rombaux, De Volder, & Renier, 2009; Rombaux et al., 2010; Renier et al., 2013; Gagnon, Ismaili, Ptito, & Kupers, 2015), mais disparaît lorsqu'on leur donne une liste de choix possible (Smith et al., 1993; Rosenbluth, Grossman, & Kaitz, 2000; Cuevas et al., 2010; Bealieu-Lefebvre, Schneider, Kupers, & Ptito, 2010; Gagnon et al., 2015). Parmi ces articles, l'un démontre que l'habileté des PNV à identifier des odeurs est fortement corrélée avec leur facilité à apprendre à nommer de nouvelles odeurs (Wakefield et al., 2004). Ces résultats suggèrent que l'avantage des PNV lors de tâche d'identification olfactive provient, du moins partiellement, d'une compensation cognitive et non pas purement perceptuelle.

Le motif des résultats est légèrement moins clair pour des tests perceptuels tels que la détection d'odeurs faibles, ou encore la discrimination de ces mêmes odeurs. Si certaines études révèlent un désavantage chez les PNV lors de ces tâches (Murphy & Cain, 1986; Smith et al., 1993), un nombre plus important démontrent une tendance vers de meilleures habiletés chez les PNV (Smith et al., 1993; Rosenbluth, Grossman, & Kaitz, 2000; Wakefield et al., 2004) ou encore une différence statistiquement significative en leur faveur (Cuevas et al., 2009; 2010; Rombaux et al., 2010; Bealieu-Lefebvre, et al., 2010; Renier et al., 2013).

En ce qui concerne la gustation, seulement deux études ont comparé les PNV aux PV. Toutes deux montrent que les PNV ont plus de difficultés que les PV à identifier les attributs (ex. sucré, salé, amer, acide) du goûter (Smith et al., 1993; Gagnon, Kuper, & Ptito, 2013).

Bref, les données supportent fortement la présence de meilleures habiletés olfactives chez les PNV et d'une diminution de la gustation chez ces derniers. Pour cette première, les effets les plus importants découlent d'une compensation cognitive, mais n'y sont pas limités.

Ensemble ces résultats supportent l'hypothèse de la compensation sensorielle, du moins pour l'olfaction.

Audition

L'ouïe est sans contredit le sens le plus étudié chez les PNV, car elle est impliquée dans un nombre important de processus pouvant être la cible d'une compensation sensorielle. Parmi ces derniers, on retrouve la localisation de sons, la perception de sons dans le bruit et la perception des voix, toutes des habiletés qui revêtent une importance particulière en absence de la vision. Similairement à l'étude du tact et de l'olfaction, l'étude de l'ouïe révèle, selon les tâches, des surperformances, parfois sujettes à controverses, chez les PNV. Toutefois, seul un court exposé des principales habiletés auditives suivra, car, considérant l'étendue de ce champ, une longue révision ne serait pas réaliste dans ce contexte.

Dès l'analyse des caractéristiques sonores basiques, les PNV présentent un avantage sur les PV; ils possèdent une meilleure résolution fréquentielle et temporelle des sons (mais voir Weaver & Stevens, 2006). Notamment, les PNV perçoivent des différences et changements de hauteur tonale plus fins que les PV (Gougoux et al., 2004; Wan, Wood, Reutens, & Wilson, 2010b) et discernent l'ordre temporel ou la durée de stimuli plus aisément (Muchnik, Efrati, Nemeth, Malin, & Hildesheimer, 1991; Gougoux et al., 2004, Weaver & Stevens, 2005; Van der Lubbe, Van Mierlo, & Postma, 2009).

Cet avantage n'est pas seulement présent pour des processus basiques, mais aussi pour des habiletés plus complexes telle la localisation sonore. La capacité à repérer la provenance d'un son est d'une importance sans pareil pour les PNV : elle leur permet de naviguer dans leur environnement. Les études sur ce sujet démontrent que les PNV localisent avec plus de précision

les sons en périphérie lors de tâche binaurale (Röder et al., 1999; Voss et al., 2004; Després, Candas, & Dufour, 2005). Plus spectaculaire encore est leur habileté à détecter correctement la provenance de sons même lorsque l'oreille ipsilatérale au son est bloquée (Lessard, Paré, Lepore, & Lassonde, 1998), une habileté qui semble découler d'un meilleur usage des indices spectraux monauraux créés par la pinna ou la tête (Doucet et al., 2005; Voss, Lepore, Gougoux, & Zatorre 2011). Étrangement, les PNV sont moins performants que les PV lorsqu'ils doivent évaluer l'élévation d'une source sonore, et ce, malgré le fait que cette habileté repose sur la perception des indices monauraux, les mêmes qui sont utilisées à meilleur escient par certains PNV lors de tâche de localisation de sons en périphérie (Zwiers, Opstal, & Cruysberg, 2001; Lewald, 2002). Des données récentes suggèrent que cette divergence résulte d'un compromis entre ces deux habiletés : les PNV qui montrent un avantage sur la périphérie sont ceux qui sont désavantagés sur l'élévation (Voss, Tabry, & Zatorre, 2015).

La perception de voix revêt également une importance particulière chez les PNV car elle leur permet d'identifier les individus qu'ils rencontrent ainsi que l'état émotionnel de ces personnes (Belin, Fecteau, & Bédard, 2004), deux habiletés nécessaires à des interactions sociales adaptées. La première étude sur ce sujet, impliquant 70 PNV, montre qu'ils sélectionnaient une voix cible parmi d'autres voix avec plus de succès que les PV (Bull, Rathborn, & Clifford, 1983). Cet avantage relié à la perception des voix, qui a été répliqué par trois études (Braun, 2012; Föcker, Best, Hölig, & Röder, 2012; Hölig, Föcker, Brest, Röder, & Büchel, 2014), mais absent de quatre autres¹ (Winograd, Spencer, & Kerr, 1984; Eladd, Segev, & Tobin, 1998; Gougoux et al., 2009), semble dépendre de la méthodologie employée. Lorsque les participants sont entraînés à

¹Une cinquième (Günzberger, Bresser, & Ter Keurs, 1987), ne comportant aucun test statistique comparant les PNV aux PV, a été exclue de cette liste.

reconnaitre de nouvelles voix, les PNV montrent un avantage sans équivoque (Braun, 2012; Föcker et al., 2012; Hölig et al., 2014). Toutefois, lorsqu'ils ont peu de temps pour les apprendre (Winograd et al., 1984) ou que les voix sont dégradées par le filtre d'un téléphone (Eladd et al., 1998; Braun, 2012), cet avantage disparaît. Bref, dans un environnement naturel (ex. pas dégradés par le filtre d'un téléphone) les PNV perçoivent mieux les voix que les PV.

En conclusion, les PNV démontrent de meilleures habiletés auditives, tant au niveau des caractéristiques de bases que pour des habiletés plus complexes. Ensemble, ces résultats supportent la présence d'une compensation sensorielle auditive chez les PNV.

Autres avantages perceptuels et cognitifs chez les PNV et conclusion finale

La revue de la littérature ci-dessus, quoiqu'exhaustive, est incomplète; les PNV se distinguent des PV sur une variété d'autres tâches perceptuelles et attentionnelles qui ne sont pas abordées par souci de brièveté. Ces dernières incluent la perception de la parole (Niemeyer & Starlinger, 1981; Muchnik et al., 1991; Hugdahl et al., 2004), l'écholocalisation (Schenkman & Nilsson, 2010), la mémoire (Požár, 1982; Hull & Mason, 1995; Röder, Rösler, & Neville, 2001; Röder & Rösler, 2003) et l'attention (Kujala, Lehtokoski, Alho, Kekoni, & Näätänen, 1997; Liotti, Ryder, & Woldorff, 1998; Röder et al., 1999; Collignon, Renier, Bruyer, Tranduy, & Veraart, 2006).

L'habileté des PNV à supplanter les PV sur une variété de tâches tant attentionnelles que cognitives en plus de leur perception et acuité accrues lors de tâches tactiles, olfactives et auditives démontre l'existence d'une compensation sensorielle. Toutefois, ces études ne révèlent pas l'origine biologique de cette compensation.

Origines cérébrales de la compensation sensorielle

Sachant que la compensation sensorielle est présente chez les PNV, il est possible d'en investiguer la source. Comme les processus perceptifs sont sous-tendus par le cerveau, il est probable que les suprahabilités des PNV découlent d'une réorganisation neuronale. Les méthodes d'imagerie cérébrale modernes (TEP : Tomographie par émission de positron, et IRMf : imagerie par résonance magnétique fonctionnelle) permettent d'étudier ce type de phénomènes et leur utilisation a éclairci les origines de la compensation sensorielle chez les PNV. En effet, en comparant les régions cérébrales activées lors de tâche sensorielle chez les PNV et les PV, des études de TEP et d'IRMf ont exposé des différences d'activité neuronale qui pourraient être à l'origine de la compensation sensorielle chez les PNV.

En 1988, Wanet-Defalque et collaborateurs ont publié une étude séminale démontrant une activité métabolique plus élevée au niveau des cortex visuels primaires des PNV. À cette époque, nul ne savait si les neurones du lobe occipital de ces derniers étaient toujours actifs. Suite à la découverte de cette activité, il a été suggéré que le lobe occipital des PNV était plastique et sujet à une réorganisation intermodale; plutôt que d'être dédié à la vision, il serait recruté lors de l'analyse d'une ou plusieurs autres modalités (audition, tact et/ou odorat). Depuis, plusieurs articles supportant cette hypothèse ont été publiés. Un nombre important de ces études démontrent que le lobe occipital des PNV est fortement activé lors de tâches auditives (Weeks et al., 2000; Poirier et al., 2006), tactiles (Sadato et al., 1996; Büchel, Price, Frackowiak, & Friston, 1998; Burton, Sinclair, & McLaren, 2004) et olfactives (Kupers et al., 2011; voir Simon-Dack, Rodriguez, & Teder-Salejarvi, 2008 pour une recension exhaustive des études d'imageries, et plus généralement, Frasnelli, Collignon, Voss, & Lepore, 2011), et que l'amplitude de cette activation est positivement corrélée avec la performance des PNV sur les

tâches effectuées (audition : Gougoux, Zatorre, Lassonde, Voss, & Lepore, 2005; Gougoux et al., 2009, olfaction : Renier et al., 2013). Cette relation n'est pas qu'un épiphénomène; la perturbation de l'activité neuronale du lobe occipital n'entraîne des chutes de performances que chez les PNV (Cohen et al., 1997; Cohen et al., 1999). Notamment, l'habileté auditive qui est affectée dépend de la région occipitale perturbée par la stimulation magnétique transcrânienne (SMT; Collignon, Lassonde, Lepore, Bastien, & Veraart, 2007). Plus précisément, de trois tâches de discrimination (intensité, hauteur et location), une seule était affectée par l'application de la SMT répétée au cortex extrastré droit. Ces résultats suggèrent fortement que l'activité neuronale du lobe occipital est fonctionnellement spécifique et localisée. Donc, la source de la compensation sensorielle n'est pas une force nerveuse abstraite, mais plutôt un recrutement neuronal « transmodal ». L'analyse des modalités non visuelles, sous-tendue par un plus grand nombre de neurones, mènerait à une perception accrue.

L'étude de la cécité à l'aide de méthodes d'imagerie modernes souligne plus que les bases cérébrales de la compensation sensorielle; elle révèle que la réorganisation cérébrale à la base des suprahabilités des PNV est sujette à une période critique. C'est-à-dire que l'importance de la réorganisation intermodale dépend de l'âge auquel la cécité survient. Après 18 ans, l'activité occipitale n'est que peu ou pas modifiée, n'est pas nécessaire aux processus sensoriels et n'est pas liée à des mécanismes compensatoires (Cohen et al., 1999; Sadato, Okada, Honda, & Yonekura, Y., 2002; Voss, Gougoux, Lassonde, Zatorre, & Lepore, 2006; Voss, Gougoux, Zatorre, Lassonde, & Lepore, 2008; voir Voss 2013 pour une revue plus exhaustive de la littérature). Cette limitation de la plasticité, la capacité à se réorganiser, souligne l'importance de distinguer entre PNV congénitaux, précoces et tardifs. Comme l'objet de la présente thèse est d'étudier la réorganisation intermodale, l'accent sera dès lors mis sur la cécité congénitale et

précoce. Cette dernière sera, à partir de maintenant, définie comme une perte de vision survenant avant l'âge de 5 ans et précédée par une vision limitée dès la naissance.

Principes de la réorganisation intermodale

Sachant que, chez les PNV précoces, le lobe occipital traite l'information de l'olfaction, du tact et de l'audition et que cela semble être fait de manière localisée et spécifique, l'étape suivante est de cartographier ces fonctions. En général, le cerveau est organisé en modules fonctionnels : des régions circonscrites se spécialisent dans l'analyse d'attributs spécifiques (p.ex. : reconnaissance de visages, Kanwisher, McDermott, & Chun, 1997; de scènes ou d'objets, Epstein et al., 1999; analyse des objets en mouvements, Zihl, von Cramon, & Mai, 1983; Lewis, Beauchamp, & De Yoe, 2000; etc). En est-il de même au niveau du lobe occipital des PNV? Si oui, quelles sont ses fonctions et où sont-elles localisées?

L'étude de Collignon et collègues (2007) fournit un indice à ce sujet. Dans cette étude, il est démontré que l'application de la SMT au cortex extrastrié dorsal droit vient perturber l'habileté des PNV à localiser des sons, tandis que cette même région est impliquée dans des processus similaires pour la vision chez les PV (Ungerleider et al., 1984; Haxby et al., 1991). Donc, il semble possible que, chez les PNV, les modules fonctionnels occipitaux maintiennent leurs fonctions générales, mais que les modalités sensorielles analysées soient différentes. Plusieurs études supportent ces idées; elles démontrent que le lobe occipital dorsal préserve sa préférence pour les tâches d'ordre spatial (Weeks et al., 2000; Vanlierde, De Volder, Wanet-Defalque, & Veraart, 2003; Collignon et al., 2011) tandis que le lobe occipital ventral reste impliqué dans des processus de reconnaissance d'objets tant tactiles qu'auditifs (Sadato et al., 1996; Büchel, Price, & Friston, 1998; De Volder et al., 2001; Pietrini et al., 2004; Burton,

McLaren, & Sinclair, 2006). Cette organisation du lobe occipital en deux voies, l'une ventrale l'autre dorsale, respectivement impliquées dans l'analyse de la nature des objets et de leurs relations spatiales, est généralement observée pour la vision (voir Ungerleider & Haxby, 1994). Ensemble, ces résultats suggèrent que le lobe occipital des PNV s'organise similairement à celui des PV.

La similarité de l'organisation cérébrale fonctionnelle des PV et des PNV ne se limite pas seulement à ces deux voies, mais s'étend aussi aux fonctions plus spécifiques. Des populations neuronales se spécialisant dans l'analyse d'un type particulier de stimuli semblent elles aussi maintenir leur fonction générale. Par exemple, le complexe temporal médian (MT/MST) est responsable de l'analyse du mouvement d'objets visuels chez les PV (Zihl, von Cramon, & Mai, 1983; Lewis, Beauchamp, & De Yoe, 2000) et du mouvements d'objets auditifs et tactiles chez les PNV (Poirier et al., 2006; Ricciardi et al., 2007; Bedny, Konkle, Pelphrey, Saxe, & Pascual-Leone; Jiang, Stecker, & Fine, 2014). L'aire extrastriée des corps montre ce même effet, répondant fortement au visionnement de différentes parties du corps chez les PV (Downing, Jiang, Shuman, & Kanwisher, 2001) et à leur touché chez les PNV (Kitada et al., 2014; Striem-Amit & Amedi, 2014). Similairement, le gyrus fusiforme, analysant les visages chez les PV (Kanwisher, McDermott, & Chun, 1997), est recruté par son équivalent auditif chez les PNV, les voix, elles aussi nécessaires à transmettre l'état émotionnel des individus et permettant leur identification (Gougoux et al., 2009; Hölig et al., 2014).

L'ensemble des études énumérées ci-dessus examine des modules fonctionnels de haut niveau, mais qu'en est-il des régions « visuelles » de bas niveau telles V1 et V2? Sont-elles organisées de manière semblable chez les PNV et les PV? Si la réponse semble positive pour les réseaux les plus étendus, elle reste évasive pour l'ensemble des modules circonscrits. En

effet, bien qu'il soit possible de retrouver chez les PNV les mêmes grandes sous-divisions occipitales (antéro-postérieur, dorsoventral et latéralisation hémisphérique) que chez les PV (Striem-Amit et al., 2015), deux modules plus spécifiques semblent posséder des topographies différentes chez les PNV (Striem-Amit et al., 2015). Toutefois, il est impossible de tirer des conclusions concernant les autres modules, car la seule étude ayant comparée la topographie de l'ensemble des modules fonctionnels occipitaux des PNV à celle des PV n'a pas identifié les loci des différences intergroupes (Hasson et al., 2015). À l'opposé, la seconde étude sur ce sujet s'est limitée à étudier V1 et V2 (Striem-Amit et al., 2015); elles sont séparées par une frontière différente chez les PNV. Similairement, les études visant à établir la fonction des régions « visuelles » de bas niveau chez les PNV démontrent qu'elles sont impliquées dans des processus langagiers (Amedi et al., 2003; Amedi et al., 2004; Cohen et al., 1997; Cohen et al., 1999; Sadato et al., 1996) ou attentionnels (Weaver & Stevens, 2007), mais elles ne comparent pas la topographie de ces modules à celle des PV. Ainsi, il est impossible de savoir si l'intégralité des modules fonctionnels de bas niveau chez les PNV est toujours présente, possédant de nouvelles fonctions, ou si de nouveaux modules se développent chez les PNV.

Bref, il semble y avoir un maintien général des fonctions des régions cérébrales chez les PNV. Notamment, la réorganisation intermodale se limiterait à une modification des entrées sensorielles des modules fonctionnels occipitaux. Toutefois, les indices supportant cette interprétation se limitent à certaines régions « visuelles » de haut niveau, tandis que les régions de bas niveau semblent maintenir leur organisation macroscopique, mais pas leurs modules fonctionnels circonscrits. Ainsi, l'influence de la cécité sur l'établissement et la topographie des modules fonctionnels chez les PNV est une question d'actualité à laquelle une réponse est requise afin de mieux comprendre les facteurs qui influencent la plasticité cérébrale.

La première expérience de cette thèse vise à explorer cette question de manière holistique afin d'examiner la topographie de l'ensemble des modules fonctionnels de haut et bas niveau chez les PNV. Ceci a été possible grâce à l'emploi de scans d'IRMf acquis à l'état de repos (ER; eng anglais resting-state, voir section suivantes pour plus de détails), car ce protocole permet exploite la nature changeante de la pensée humaine afin de cartographier les modules et réseaux présents dans le cerveau (voir van den Heuvel & Hulshoff Pol, 2010). De pair avec une nouvelle méthode développée pour cette expérience, nous avons pu mesurer des différences intergroupes (PV et PNV) dans la topographie des modules visuels.

Intégration sensorielle, état de repos et plasticité

Bien que le cerveau soit organisé en modules fonctionnels, ceux-ci ne sont pas indépendants; ils s'influencent l'un l'autre et forment des réseaux qui sous-tendent la perception et la cognition. Cette communication interrégionale, ou intégration fonctionnelle, est considérée comme étant nécessaire à « orchestrer la symphonie d'émotions, de perceptions, de pensées et d'actions² » qui résultent des processus neuronaux (Varela, Lachaux, Rodriguez, & Martinerie, 2001). Alors, qu'advient-il de cette communication suite à la réorganisation cérébrale induite par la cécité? Reste-t-elle inchangée ou est-elle aussi modifiée? La réponse à cette question est cruciale afin de comprendre le rôle qu'ont les différents modules occipitaux des PNV dans les réseaux complexes du cerveau. Pour bien cerner cette question, il faut d'abord connaître les méthodes qui sont employées chez l'humain pour mesurer l'intégration fonctionnelle.

Mesurer l'intégration fonctionnelle

² Traduction libre de Varela, Lachaux, Rodriguez, & Martinerie, 2001

Deux grandes méthodes existent pour mesurer la communication interrégionale du cerveau : la connectivité structurelle et la connectivité fonctionnelle (CF). La connectivité structurelle évalue l'existence et l'intégrité de tracts d'axones entre deux régions (Assaf & Pasternak, 2008), tandis que la CF mesure l'influence d'une région sur une autre (Friston 2003). Cette distinction est critique, car, bien qu'il existe une correspondance entre les deux types de connectivités (voir van den Heuvel & Hulshoff Pol, 2010), une région peut tout de même communiquer avec une autre par l'intermédiaire de plusieurs modules relais. Ainsi, la CF possède l'avantage de pouvoir déterminer quelles régions cérébrales vont, ensemble, former un réseau distinct qui supportera une fonction spécifique.

L'IRMf est l'une des méthodes de pointe pour évaluer la CF chez l'humain. Elle permet d'imager les variations du flot sanguin du cerveau, une mesure représentative de l'activité neuronale (Logothetis & Wandell, 2004), à une résolution élevée (1-3 mm³). À partir de ce type de données, il est possible d'évaluer le degré de CF de plusieurs manières, la plus simple étant de corrélérer l'activité moyenne d'une région cérébrale à chacune des autres régions du cerveau. Deux régions dont l'activité démontre une forte corrélation seront considérées comme ayant une forte CF tandis que des régions dont l'activité est faiblement corrélée seront considérées comme étant peu ou pas connectées.

Bien que la CF puisse être mesurée lorsque les participants effectuent une tâche cognitive précise (ex. écoute d'une vidéo, discrimination de stimuli, tâche motrice, etc.), permettant d'observer les réseaux cérébraux impliqués lors de cette dernière, cette méthode a été quelque peu délaissée en faveur de mesures prises lorsque les participants sont libres de penser à ce qu'ils désirent. Cet *état de repos* (voir van den Heuvel & Hulshoff Pol, 2010), quoiqu'à première vue singulier, est un outil extrêmement versatile et fiable (Van Dijk et al., 2010). En effet, à

l'intérieur d'une seule séance d'ER (5-10 minutes), il est possible de mesurer la CF entre l'ensemble possible des régions cérébrales. La validité de cette mesure est supportée par la forte correspondance entre les réseaux cérébraux cartographiés à l'aide l'ER et ceux qui sont mobilisés lors d'une variété de processus cognitifs et perceptuels (Cordes et al., 2000; Smith et al., 2009; Wig et al., 2014). Cette correspondance résulte de la distinctivité des décours temporeux de chacun de ces réseaux. Spécifiquement, à l'intérieur d'une seule séance d'ER, le cerveau entrera subséquent plusieurs modes cognitifs différents (Deco, Jirsa, & McIntosh, 2011; Karanoglu et al., 2013; Smith et al., 2012) chacun représentatif d'un réseau différent et possédant un motif de connectivité distinct. Ainsi, mesurer la CF à l'ER est avantageux, car elle peut être facilement obtenue à partir de courts scans cérébraux et est représentative de l'association moyenne entre les différentes régions cérébrales.

État de repos et connectivité fonctionnelle chez les PNV

À l'aide de protocoles d'ER, plusieurs études ont investigué l'influence de la cécité précoce ou congénitale sur l'intégration fonctionnelle. Ces études révèlent que la CF du lobe occipital des PNV est modifiée. On retrouve une forte diminution de nombreuses connexions occipitales inter-hémisphériques et une augmentation des connexions occipitales intra-hémisphériques (Burton et al., 2014; Liu et al., 2007; Yu et al., 2008). De plus, il semble y avoir une augmentation de la connectivité occipito-frontale chez les PNV, supportant le rôle des lobes occipitaux dans des processus mnésiques ou attentionnels (Burton et al., 2014; Striem-Amiet et al., 2015). Plus intrigants encore sont les rapports d'une baisse de connectivité entre le lobe occipital et les cortex sensoriels primaires auditifs et tactiles (Bedny et al., 2011; Burton et al., 2014; Liu et al., 2007; Qin et al., 2013; Striem-Amiet et al., 2015; Yu et al., 2008; voir Bock and

Fine, 2014 pour une revue récente du sujet). La fiabilité de cet effet à l'ER contraste fortement avec les études, présentées dans la section précédente (Origines cérébrales de la compensation sensorielle), qui démontrent un recrutement de cortex occipital lors de tâches auditives et tactiles chez les PNV. De pair avec la démonstration d'une plus forte CF entre les régions frontales attentionnelles/langagières et l'occiput chez les PNV, ces résultats renforcent la vision selon laquelle certaines régions du lobe occipital ne sont pas impliquées dans l'analyse sensorielle du tact et de l'audition, mais plutôt dans des processus de haut niveau (p. ex. attention).

Donc, déterminer la source de cette contradiction entre les études d'ER et d'activation est nécessaire afin de désambiguïser le rôle des lobes occipitaux chez les PNV : ne sont-ils réellement qu'impliqués dans l'attention et pas dans les processus sensoriels plus basiques? Afin de répondre à cette question, il est nécessaire d'examiner la contradiction qui existe entre les résultats des études de CF et celles d'activation (voir Origines cérébrales de la compensation sensorielle). Pour ce faire, il est essentiel de mesurer la CF à l'ER ainsi que lorsque les participants sont occupés par des tâches spécifiques. Ce problème est abordé par le deuxième article de cette thèse. Spécifiquement, la CF à l'ER et durant une tâche a été mesurée chez des PNV et PV et ensuite comparée, permettant d'identifier la source de la contradiction entre les études de CF à l'ER et celles d'activation.

Objectifs et hypothèses de recherche

L'objectif de cette thèse est d'examiner l'effet de la cécité précoce sur l'intégration et la topographie fonctionnelle du lobe occipital. Afin d'atteindre ces objectifs, trois études différentes ont été élaborées. Les deux premières emploient des enregistrements d'IRMf à l'état de repos afin d'examiner l'intégration fonctionnelle ainsi que la topographie des modules

fonctionnels des lobes occipitaux. Suivant les résultats des deux premières études, qui révèlent une forte réorganisation des pôles occipitaux chez les PNV, il devient nécessaire d'examiner les fonctions de ces régions. Pour cela, la troisième étude vient valider une méthodologie permettant d'utiliser des stimuli auditifs complexes (voix humaines) afin d'examiner les fonctions des pôles occipitaux ainsi que la réorganisation cérébrale à la base de la perception des voix chez les PNV.

Premier article : Localisation fonctionnelle : topographie des modules fonctionnels chez les PNV.

Le premier article de cette thèse vise à examiner la topographie des modules fonctionnels « visuels » chez les PNV. La majorité des études récentes portant sur les fonctions du lobe occipital chez les PNV ont tenté d'étudier les similarités entre les PNV et les PV, tant au niveau des modules fonctionnels circonscrits qu'au niveau des réseaux. Toutefois, elles n'examinent qu'un nombre restreint de modules connus et rarement la topographie exacte de ces derniers. Il est essentiel d'investiguer cette différence afin de comprendre l'effet qu'a la cécité sur la formation de modules fonctionnels. Ceci est particulièrement vrai pour les modules visuels de bas niveau auxquels de nouvelles fonctions sont attribuées chez les PNV, mais dont la correspondance avec des modules visuels connus reste ambiguë. Résoudre cette question permettra d'élucider les mécanismes à la source de la formation de modules fonctionnels.

La topographie des modules fonctionnels a été mesurée à partir de numérisations d'IRMf acquises à l'ER chez les PNV et les PV. Le choix méthodologique d'utiliser l'ER repose sur des études qui démontrent que cet état permet de cartographier les réseaux cérébraux. De plus, l'ER permet d'investiguer l'ensemble des modules fonctionnels de manière holistique. Après acquisition, les données ont été soumises à un algorithme de partitionnement afin d'extraire des

régions dont l'activité est homogène et qui sont maximale­ment ségréguées des autres. Ces partitions, constituant une approximation des modules/réseaux fonctionnels sous-jacents, ont ensuite été comparées entre les groupes à l'aide d'un indice de similarité éprouvé, le coefficient de Sørensen et Dice (Dice, 1945; Sørensen, 1948), et adapté pour la première fois à l'analyse de partitions cérébrales. Les analyses ont été conduites à plusieurs résolutions différentes afin de capter à la fois des différences au niveau des grands réseaux ainsi que celles des modules circonscrits.

Hypothèses de recherche

Première hypothèse : En accord avec les résultats d'études démontrant une organisation similaire des fonctions chez les PNV et les PV, les cortex « visuels » associatifs (c.-à-d. de haut niveau), devraient être sous-divisés en partitions similaires chez les PNV et les PV.

Deuxième hypothèse : Suivant les résultats d'études démontrant l'acquisition de nouvelles fonctions et une forte modification des motifs de connectivité des régions « visuelles » primaires et secondaires chez les PNV, ces régions devraient présenter un motif de partitions différent.

Deuxième article : Intégration fonctionnelle : effet de l'état cognitif sur connectivité fonctionnelle à l'état de repos chez les PNV.

Cette expérience a été élaborée afin d'étudier les différences d'intégration fonctionnelle entre les PNV et les PV, spécifiquement, la contradiction qui existe entre les études d'activation et d'ER en ce qui a trait à la communication entre lobes occipitaux et les cortex sensoriels primaires. Brièvement, la CF à l'ER entre les lobes occipitaux et les aires sensorielles primaires est diminuée chez les PNV ce qui met en doute l'implication des lobes occipitaux dans l'analyse sensorielle du tact et de l'audition observée par les études d'activations, ainsi que la validité de la CF mesurée à l'ER.

Il a récemment été démontré que l'état cognitif des participants peut influencer la CF et que cette influence peut varier selon la population testée (Çetin et al., 2014; Nair et al., 2014). Nous avons donc postulé que la contradiction observée entre les études de CF et d'activation était causée par des différences d'états cognitifs entre ces études. En effet, lors des études d'ER, la pensée des participants est libre d'errer tandis que lors des tâches d'activations, les participants se concentrent sur une tâche bien précise. Afin d'examiner le postulat, les participants ont été scannés par IRMf lorsqu'ils étaient à l'état de repos et durant une tâche auditive. La CF a ensuite été mesurée durant ces deux états cognitifs (repos et tâche) de la même manière afin de vérifier l'adéquation des mesures prises au repos et lors de la tâche.

Si le précédent postulat est vérifié, il reste à expliquer les différences de CF à l'ER entre les PNV et les PV. Une piste d'exploration provient d'études qui démontrent que l'utilisation d'une seule valeur de CF entre deux régions cérébrales obscurcit le fait que chaque région cérébrale est impliquée dans plusieurs modes cognitifs (Hutchison et al., 2013a; 2013b; Smith et al, 2012). Plus une région est impliquée dans un grand nombre de ces modes, moins sa CF

avec une région précise sera représentative, car elle sera plus fortement noyée par les autres modes. Ainsi, la diminution de CF occipito-temporale à l'ER chez les PNV pourrait résulter d'une participation des lobes occipitaux à un plus grand nombre de modes cognitifs. Donc, la CF occipito-temporale a aussi été mesurée à l'intérieure de courtes fenêtres temporelles (quelques secondes au lieu de plusieurs minutes) et la variabilité de cette CF chez les PNV comparée à celle des PV.

Hypothèses de recherche

Première hypothèse : Si la contradiction entre les études de CF à l'ER et les études d'activations est causée par des différences d'états cognitifs entre ces types d'études, alors l'état cognitif devrait moduler différemment la CF occipito-temporale chez les PNV que chez les PV. Autrement dit, la CF occipito-temporale devrait être plus basse chez les PNV à l'ER et augmenter lors de la tâche auditive. À l'opposé, la CF devrait être plus élevée chez les PV à l'ER et diminuer ou maintenir sa force lors de la tâche auditive.

Deuxième hypothèse : Si la diminution de CF occipito-temporale à l'ER chez les PNV est causée par une participation des lobes occipitaux à un plus grand nombre de modes temporeux que chez les PV, alors, cette CF devrait être plus variable à travers le temps chez les PNV.

Troisième article : Mesurer la perception de voix dans le bruit afin d'en ajuster la difficulté.

Le troisième article de cette thèse a été élaboré afin de faire suite aux résultats des deux premiers. Spécifiquement, les premier et deuxième articles révèlent, au sein des pôles occipitaux dorsaux des PNV, l'existence d'un module possédant des caractéristiques fonctionnelles fortement différentes comparées à celles de PV. Notamment, la fonction exacte de cette région des pôles occipitaux chez les PNV reste méconnue; quoique plusieurs études mettent en évidence le rôle de la région ventrale des pôles occipitaux dans des processus langagiers (Amedi et al., 2003; Amedi et al., 2004; Sadato et al., 1996), la fonction de son aspect dorsal est évasive. Toutefois, grâce aux résultats des deux premières études de cette thèse, il est possible d'émettre des hypothèses à ce sujet.

L'une des hypothèses avancées dans le deuxième article de cette thèse est que les pôles occipitaux sont multimodaux, analysant à la fois le tact et l'audition à l'aide de populations neuronales qui se chevauchent. Cette caractéristique serait encore méconnue, car le chevauchement mentionné ci-dessus ne serait apparent que lorsqu'une condition sensorielle est comparée au silence, une étape rarement effectuée chez les PNV (mais voir Renier et al., 2010). Afin d'approfondir notre compréhension de cette région cérébrale chez les PNV, il est nécessaire d'étudier leur réponse à des stimuli auditifs et tactiles simples et complexes. Comme la discussion sur la compensation sensorielle le démontre, la voix humaine est l'un des stimuli les plus pertinents à étudier chez les PNV. En effet, elle contient non seulement l'information nécessaire à l'identification d'un individu, mais aussi, chez les PNV, son analyse est sous-tendue par des cortex « visuels » qui sont sujets à la plasticité intermodale (Gougoux et al., 2009; Hölig et al., 2014). Donc, si les pôles occipitaux répondent à certains stimuli auditifs complexes, ils seront le plus probablement mobilisés lors de l'analyse de voix.

Afin de poursuivre cette avenue de recherche et de procéder à des tests chez les PNV, il était nécessaire d'élaborer des méthodes de présentations de stimuli. En effet, des études démontrent que les différences d'activations neuronales entre deux populations peuvent être causées par une différence de performance sur une tâche. De surcroît, il a été démontré que les PNV performant mieux que les PV lors de tâches de reconnaissance vocale. Le troisième article de cette thèse présente une méthode qui permettrait d'éviter le biais induit par ces différences en égalisant la difficulté d'une tâche de reconnaissance de la voix, un phénomène particulièrement difficile à mesurer.

Au-delà de permettre l'ajustement de paramètres afin de maintenir un certain niveau de difficulté, la tâche a aussi été élaborée afin d'étudier les processus responsables de la perception et la mémoire explicite et implicite des voix. Comme ces processus implicites n'ont pas été étudiés chez les PNV et restent encore méconnus chez les PV, l'utilité potentielle de la méthode développée ici s'en voit accrue. Pour cet article, nos hypothèses et méthodes découlent d'études qui ont démontrés que lorsqu'une énonciation est prononcée par une voix connue de l'auditeur, cette énonciation est plus rapidement/facilement analysée ou reconnue (Nygaard, Sommers & Pisoni, 1994; Nygaard & Pisoni, 1998; Yonan & Sommers, 2000; Pilotti, Beyer, & Yasunami, 2001; Souza, Gehani, Wright, & McCloy, 2013). Plus récemment, plusieurs études ont suggéré que cet effet prenait place même lorsque le locuteur n'est pas explicitement identifié par les participants (Yonan & Sommers; Newman & Evers, 2007; Souza et al., 2013). Toutefois, ces études n'ont pas réussi à masquer l'identité des locuteurs, mettant en doute leurs résultats. Bref, et plus précisément, le principal apport théorique visé par ce troisième article est de vérifier la dépendance de la perception de voix familières sur l'identification du locuteur et sur la prise de conscience que les stimuli entendus sont des voix humaines.

Afin de répondre à ces questions chez les PV, des paires de stimuli composées chacune d'une voix et d'une note de piano ont été présentées à des PV. Ces derniers devaient discriminer les deux sons. Ceci était fait en présence de bruit afin que la tâche soit relativement difficile. Parmi les voix présentées, le quart provenait d'une personne personnellement connue des participants. Dans une condition, les participants n'étaient pas informés de la présence de voix familières, dans la seconde condition, ils n'étaient pas informés que des voix seraient présentées.

Hypothèses de recherche

Première hypothèse : Si l'avantage relié à la perception des voix ne dépend pas de l'identification du locuteur, alors les voix familières seront plus facilement discriminées des notes de piano que les voix familières, et ce, même lorsque le locuteur familier n'est pas reconnu par les participants.

Deuxième hypothèse : Similairement, si l'avantage relié à la perception des voix ne dépend pas de connaissances a priori concernant le type de stimuli présentés, alors les voix familières seront plus facilement discriminées des notes de piano que les voix familières, et ce, même lorsque le locuteur familier n'est pas informé qu'il entendra des voix.

Articles de la thèse

Article #1

Contribution des auteurs

Maxime Pelland: Rédaction de l'article, analyse des données et conceptualisation de l'étude.

Franco Lepore: Conceptualisation de l'étude et financement en tant qu'investigateur principal.

Pierre Bellec: Conceptualisation de l'étude.

Olivier Collignon: Rédaction de l'article, conceptualisation de l'étude, collecte des données et
financement.

Topography of functional modules and networks following early-blindness

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Abstract

Recent studies have shown the brain of early-blind individuals (EB) and sighted controls (SC) to possess remarkably similar functional modules. Even “visual” regions tend to maintain their specialization by reorienting their responses to new sensory modalities. However, these findings are not ubiquitous and seem segregated to higher “visual” areas. In contrast, less is known about the mapping and topography of lower visual cortices and whether they support new modules in EBs. To investigate this issue, we developed a new holistic, data-driven, and *a priori* light method which allowed to divide our participants’ visual cortices into functionally homogeneous clusters, and to compare the topography of these clusters across EBs and SCs. Importantly, the method allows to unveil modules which are specific to a group. A group of EBs and one of SCs were scanned while their mind was left to wander. This resting-state data was submitted to clustering at multiple resolutions (from networks to circumscribed modules), and compared between groups using the Sørensen-Dice coefficient. Results are congruent with multiple findings of maintained module topography across groups and increased segregation between ventral and dorsal areas in EBs. Crucially, results also demonstrate for the first time the existence of a functionally segregated, and possibly novel brain area, within EBs’ dorso-occipital poles. Thus, our results promote the view that the establishment of segregated functional modules in occipital regions is partly, but not fully, dependent upon visual experience.

Highlights

- 1) Early-blindness impacts the brain's functional organization.
- 2) Still, topography of modules is partly similar between blind and sighted people.
- 3) A holistic method was developed to test the extent of this reorganization.
- 4) A new functional module might exist within blind people's occipital poles.
- 5) The replication of results from multiple studies validates our method.

Keywords: fMRI, early-blindness, resting-state, topography, functional modules

1. Introduction

The study of people deprived of sensory information early in life represents a unique model to investigate how sensory experience shapes the structural and functional architecture of the brain (Frasnelli, Collignon, Voss, Lepore, 2011; Heimler, Weisz & Collignon, 2014; Ricciardi et al., 2014; Striem-Amiet et al. 2015). In the last two decades, research carried with congenitally- and early-blind individuals (EBs) have shed new lights on the old ‘nature versus nurture’ debate regarding brain development by demonstrating the cerebrum’s remarkable plasticity: regions dedicated to processing visual stimuli in sighted controls (SC) are reorganized to analyze auditory and tactile stimuli in EBs (for reviews, see: Dormal and Collignon, 2011; Reich, Maidenbaum and Amedi, 2012; Ricciardi et al, 2014). To further understand the breadth of cerebral plasticity, it is paramount to examine its effect upon the development of functionally specific and homogeneous brain regions [functional modules and networks (FM/N)]. However, most recent research with EBs has focused on investigating the properties of a few FM/Ns, leaving many still to be discovered and studied, the exact differences in their topographies (e.g. layout, shape, or size) unknown.

Of the FM/Ns studied in EBs, most evidence remarkably similar functions to those of SCs: areas involved in motion (hMT+/MST: Poirier et al., 2006; Ricciardi et al., 2007; Bedny, Konkle, Pelphrey, Saxe, & Pascual-Leone, 2010; Jiang, Stecker, & Fine, 2014), body shape (extrastriate body area: Kitada et al., 2014; Striem-Amit & Amedi, 2014), identity (fusiform face area: Gougoux et al., 2009; Hölig et al., 2014), words (visual word form area: Reich et al., 2011), tools (lateral occipito-temporal cortex: Peelen et al., 2013), and spatial perception (Collignon et al., 2011) have all been shown to retain similar functional tuning (for a review, see Ricciardi et al., 2014). Crucially, studies investigating the integration of occipital regions

into large-scale brain networks have proposed that EBs and SCs share similar patterns of functional connectivity (Heine et al., 2015; Striem-Amit et al., 2015). For example, several studies have documented a maintained pattern of resting-state functional connectivity (RSFC) between functionally specific occipital regions (e.g. the visual word form area, the numerical form area, the parahippocampal place area) across blind and sighted individuals (Abboud et al., 2015; He et al., 2013; Reich et al., 2011). Butt and colleagues (2013) found that the RSFC patterns of any given blind participant were as similar to those of the sighted group as they were to the blind group, suggesting no unique reorganization in the blind. Similarly, Striem-Amit and colleagues (2015) reported that RSFC of visual cortex in blind manifests typical “retinotopic” organization principles found in sighted (differentiation by eccentricity, laterality, and elevation), with little evidence for differences between the two populations. Merging the observation of maintained functional specialization and integration in EBs’ occipital cortex, it was proposed that the inherited pattern of functional connectivity between occipital and other brain regions dictate the computation of a specific cognitive operation. Together, these studies suggest little differences between EBs and SCs in the layout of FM/Ns.

However, findings of maintained functional architecture within the occipital lobe following early or congenital blindness contrast with the numerous studies showing that early visual deprivation triggers massive “crossmodal” reorganization of the sensory tuning of occipital cortex (Cohen et al., 1997; Frasnelli et al., 2011), specific response to cognitive operation typically independent of occipital function (e.g. language; Bedny et al., 2011) and a large scale reorganization of structural and functional brain connectivity (Boldt et al., 2014; Collignon et al., 2011; 2013; Hasson et al., 2016; Klinge et al., Liu et al., 2007; Qin et al., 2013; Shimony et al., 2006; Wittenberg et al., 2004; Yu et al., 2008).

To summarize, there appears to be high similarity in the organization within occipital regions of blind and sighted, which is consistent with the notion that central aspects of its organization are independent of visual experience. However, there are also some organizational differences. Interestingly, it was recently proposed that the maintained pattern of functional organization in EB holds true only for specific high-order networks and is not found in primary visual regions like V1 (Bi, Wang, & Caramazza, 2015; Wang et al., 2014; but see Stream-Amit et al., 2015). Still, the functional subdivisions of the occipital lobe have not been systematically investigated yet: studies either limit their investigation to differences in a-priori large scale networks (Striem-Amit et al., 2015), or in identifying a difference between EBs and SCs without specifying the exact locus of the differences (Boldt et al., 2014; Hasson et al., 2016). This leaves the layout of EBs functional FM/Ns unknown.

Thus, mapping of EBs' FM/Ns is limited to a few specific ones, for which the exact topographical differences are uncharacterized. Furthermore, the reliance of most of these studies on a careful selection of stimuli to induce neuronal activity precludes the study of novel FM/Ns in EBs, greatly limiting the investigation on this topic. A way to study the topography of both known and unknown FM/Ns is to use holistic and data driven analyses which do not require specific stimuli or design to highlight FM/Ns. One such method relies on the use of resting-state (RS) data. Recorded with fMRI protocols while participants let their mind wander, RS data is defined by spontaneous fluctuations in the BOLD signal thought to be instantiated by the transient exploration of different networks (Deco, Jirsa, & McIntosh, 2011). Brain networks having distinct temporal courses, a single recording session is enough to separate them. Thus, based on these DM/Ns specific and spontaneous fluctuations, RS data can be used to group voxels with similar functional profiles into homogenous functional brain modules or networks.

The validity of such method is supported by the consistency of their results: multiple data driven multivariate techniques applied to RS data reliably identify major brain networks (Salvador et al. 2005; Beckmann et al., 2005; Damoiseaux et al., 2006; van de Heuvel et al., 2008; Bellec et al., 2010; Yeo et al. 2011). They include visual, sensorimotor, auditory, default-mode, attentional and mesolimbic, all consistent across subjects and methods. Interestingly, these large-scale RS networks can be further decomposed into subnetworks and functional modules (Salvador et al. 2005; Smith et al. 2009; Yeo et al. 2011) with potentially hundreds of functionally relevant brain regions (Bellec et al. 2010), making RS data especially useful to assess FM/Ns across both large networks and local functional modules. To our knowledge, only two studies have employed similar methods to study FM/Ns topographies in EBs, though one relied on anatomical correlations (Chen et al., 2008) rather than RS, and both have showed group differences (Boldt et al., 2014; Hasson et al., 2016). Still, due to methodological limitations, the authors were unable to discover and quantify the exact loci of the differences, making it impossible to illustrate the extent of the impact vision-loss has upon FM/Ns development.

The present study investigated the influence of vision upon the development of functional modules and networks (FM/Ns) within regions usually involved in visual processes. To do so, we acquired RS data from EBs and SCs, and decomposed them into a hierarchy of clusters. The resulting clusters were taken as proxies for FM/Ns, and their topography compared between groups. Our method distinguishes itself from that of previous studies in that it uses clustering based metrics while being holistic, data-driven, and, crucially, allowing to quantify and map how each clusters differed across the two groups. Thus, subdivisions of all “visual” cortices is done without relying on specific stimuli or design choice, nor does it make assumptions about the resolution at which clusters are most representative of functional modules.

But, crucially, it allows to investigate the exact locus of group differences in functional module topographies.

Our goal was therefore to obtain novel findings onto the “modular” organization of occipital clusters in the early blind versus sighted people. Our a priori hypothesis was that primary occipital regions (e.g. V1-V2) may show highly reorganized functional clusters while other more “high-level” regions (e.g. Parahippocampal regions) may show a pattern more similar between the two groups (Bi, Wang, & Caramazza, 2015).

2. Materials and Methods

2.1 Participants

The data of fourteen EBs [4 females, age range 27 - 61 (mean \pm SD, 42 \pm 11)] and 17 SCs [8 females, age range 23 - 60 (mean \pm SD, 39 \pm 14)] were included in the analyses (see supplementary table 1 for more information on the blind participants). Both groups were blindfolded throughout the fMRI acquisition. None of the EBs had ever had functional vision allowing pattern recognition or visually guided behavior. At the moment of the testing, all EBs were totally blind except for one who had only rudimentary sensitivity for brightness with no pattern vision. In all cases, blindness was attributed to peripheral deficits with no neurological impairment. All of the procedures were approved by the research ethic and scientific boards of the Centre for Interdisciplinary Research in Rehabilitation of Greater Montreal and the Quebec Bio-Imaging Network. Experiments were undertaken with the understanding and written consent of each participant.

2.2 General experimental design

Participants underwent a 5 minutes (136 volumes) resting-state acquisition. While in the scanner, participants were instructed to relax, not to think about anything in particular and to keep their eyes closed.

2.3 Data acquisition and preprocessing

Functional time-series were acquired using a 3-T TRIO TIM system (Siemens) equipped with a 12-channel head coil. Multislice T2*-weighted fMRI images were obtained with a gradient echo-planar sequence using axial slice orientation [time to repetition (TR) 2,200 ms; time to echo (TE) 30 ms; functional anisotropy (FA) 90°; 35 transverse slices; 3.2-mm slice thickness; 0.8-mm interslices gap; field of view (FoV) 192 × 192 mm²; matrix size 64 × 64 × 35; voxel size 3 × 3 × 3.2 mm³]. The four initial scans were discarded to allow for steady-state magnetization.

A structural T1-weighted 3D magnetization prepared rapid gradient echo sequence (voxel size 1 × 1 × 1.2 mm³; matrix size 240 × 256; TR 2,300 ms; TE 2.91 ms; TI 900 ms; FoV 256; 160 slices) was also acquired for all participants.

The datasets were analyzed using the NeuroImaging Analysis Kit (NIAK; <http://www.nitrc.org/projects/niak/>; <https://code.google.com/p/niak/>; Bellec et al., 2012) and the Minc toolkit (<http://www.bic.mni.mcgill.ca/ServicesSoftware/ServicesSoftwareMincToolKit>), and under CentOS with Octave (<http://gnu.octave.org>). All analyses were executed in parallel on the "Mammouth" supercomputer (<http://www.rqchp.ca/fr/access-aux-ressources/serveurs/mp2>), using a pipeline system for Octave and Matlab (PSOM 1.0) (Bellec et al., 2012).

Time-series were corrected for inter-slice differences in acquisition time and rigid body motion. The mean motion-corrected volume of functional data was coregistered with the T1 individual scan, which was itself non-linearly transformed to the Montreal Neurological Institute (MNI) non-linear symmetric template (Fonov et al., 2009; Fonov et al., 2011). Functional volumes were resampled to MNI space at a 3mm isotropic resolution. To minimize artifacts due to excessive motion, some time frames were removed (see method below). Afterward, slow time drifts (high-pass filter with a 0.01 Hz cut-off), the average signals in conservative masks of the white matter and the lateral ventricles, and the first principal components (95% energy) of six rigid-body motion parameters and their squares were regressed out of the time series. Finally, the volumes were spatially smoothed with a 6mm Gaussian kernel. The removal of time-frames mentioned above followed the scrubbing method of Power and colleagues (2012). This allows to rule out the possibility that the variability in the data can be accounted for by inter-subject differences in head motion by removing volumes with excessive motion (frame displacement greater than 0.5 mm).

2.4 Functional mask of “visual” cortex

A functional mask of the occipital and ventro-posterior temporal cortices, and thus encompassing most “visual” cortices, was extracted in the same fashion as in Pelland et al. (2016). This step was necessary to circumscribe subsequent analyses to a functionally homogenous macro-metric region, a criteria not necessarily met by anatomical segmentation (Zalesky et al. 2010; Park et al., 2013).

The first step to obtain the “visual” map was to reduce the computational burden of the subsequent cluster analysis by deriving ~1,000 regions (called atoms and controlled in size with

a maximal threshold of 1000 mm³) covering the cerebral grey matter. To do so, a region-growing algorithm (Bellec et al. 2006) was used and applied on the voxelwise fMRI time-series. Then, a cluster analysis was applied on the atom averaged fMRI time series to identify clusters of atoms which consistently exhibited similar fluctuations in individual subjects, and were spatially stable across subjects. This analysis was carried out using the Bootstrap Analysis of Stable Clusters (BASC) framework (Bellec et al. 2010). To summarize, the final clusters were composed of atoms with a high average probability of being assigned together across bootstrap samples. The algorithm was set *a priori* to extract exactly six clusters: that number had been shown to group regions involved in visual processes into a single cluster (unpublished data similar to those of Yeo et al. 2011). From the solution provided by the BASC, the cluster that encompassed the occipital lobe was selected as the functional mask for all subsequent analyses. Briefly, this cluster was roughly delimited by the parieto-occipital sulcus, the posterior middle temporal gyrus and the mid-section of the fusiform gyrus (see Fig 1).

2.5 Data analysis

2.5.1 Visual cortex partitioning into random atoms

The first step of the analysis was to re-divide the brain into atoms. In this iteration, the clustering was carried solely on voxels found within the “visual” mask, and grouped voxels based on spatial proximity rather than the similarity of their time-series. This step was crucial to ensure that avoid introducing biases in the following clustering step. Indeed, grouping voxels into atoms which were functionally homogeneous across group would have been anathema to our goal of finding differences between EBs and SCs.

First, the AAL template (Tzourio-Mazoyer et al., 2002) was used to seed the “visual” mask with ~400 seeds with each regions of the AAL template containing a number of seeds proportional to its size. This step ensured that the starting seeds were approximately equally distributed within the mask. Then, over multiple iterations, seeds were each grown until each voxel within the mask was part of an atom. Constraints were put on the algorithm so that voxels within an atom were contiguous and formed a roughly spherical region. Only grey matter voxels found within the functional “visual” mask were submitted to the process. Furthermore, each atom was circumscribed to one of the two cerebral hemisphere. This effectively separated the left and right “visual” cortices into 200 atoms each.

2.5.2 Clustering of atoms into functional clusters

Since dividing the “visual” mask into more than 200 atoms was unlikely to reveal low-resolution modules of interest (e.g. V1, MST, or similar modules), atoms were grouped into larger clusters using BASC (Bellec et al. 2010). In contrast with the original method, we did not extract clusters at the group level, but for each participant separately. This step was necessary for obtaining inter-subject variability, and thus, quantifying group differences. Furthermore, to avoid *a priori* biasing the selection of the number of functional cluster to extract, we used a multiresolution approach to divide the “visual” mask into a range of resolutions (3 to 25 clusters per hemisphere) rather than a single one. Thus, we obtained 23 clustering solutions for each participant with low resolution indexing large networks and high resolution clusters being more akin to circumscribed functional modules.

To summarize our method, for each participant, a circular block bootstrap (Efron & Tibshirani, 1994) was applied to extract 100 surrogate time-series from each participant. Each

surrogate time series is then submitted to a hierarchical agglomerative algorithm using the Ward criterion. From this, clustering schemes at each studied resolution are extracted. Iterations of the clustering solution within a resolution are averaged to obtain a stability matrix that indexes the likelihood that two atoms will be grouped into the same cluster. For each participant, the resulting stability matrix is submitted to a hierarchical agglomerative clustering scheme (using the Ward criterion) to extract the clustering solution most representative of that participant's surrogate time series (see Bellec et al., 2010). The resulting clusters were then submitted to the analyses described in the next section.

For visualization purposes only, we also used BASC to obtain a group clustering solution at each resolution (Supplementary figure 1). A full description of the method can be found in Bellec and colleagues (2010).

2.5.3 Individual cluster comparison across groups

The Sørensen-Dice coefficient (Dice 1945; Sørensen, 1948), an index of similarity between two samples, was used to compare the topography of clusters between groups. This was done at each resolution separately by comparing the clustering scheme of each EB participant to that of every other participant, including other members of the EB group. For each of these pairs of participants, the coefficient was measured for every atom, comparing the overlap of the clusters to which the atom belonged to in one participant to the one it belonged to in the other. The calculation of the coefficient between two participants and for atom v , SDC_v , is formally described by the following equation:

$$SDC_v = \frac{2c}{a + b}$$

where c is the number of voxels belonging to the same cluster as v in both participant, a is the number of voxels which are part of the same cluster as v in one of the participants, and b is the number of voxels which are part of the same cluster as v for the other participant.

In summary, for every EB participant, a SDC was obtained with every other EB participant (within-group SDC), and with every SC participants (between-group SDC). This resulted in 13 within-group SDC and 17 between-group SDC for every EB participant. For each atom and EB participant, the mean of all between and within SDC were computed, effectively indexing how each EB's clustering scheme resembled, on average, that of the other EBs (within-group SDC average) and that of the SCs (between-group SDC average).

Atom-wise statistical comparisons of the participant-averaged SDC was done using a paired sampled t-test. The resulting p -values indicate the likelihood of an atom belonging to clusters that are similar within the EB group, and dissimilar between the EB and SC groups. Differences in network topographies were deemed significant for a $p < .05$ (with Bonferonni correction). Since it is impossible to evaluate which resolution is most representative of FM/Ns, tests were not carried independently at each of the 23 resolutions. Instead, we used an omnibus test in which SDC values (within- and between-group SDC average) were averaged across resolutions. This test highlights group differences in clustering that are strong across resolutions without assuming which is the most representative of FM/Ns. To overshadow our results, results collapsed across all resolutions were partly dependent upon large modules. To study differences in local functional modules, we decided to investigate differences in SDCs at high resolutions separately from lower ones. Again, we employed an omnibus test, but instead of pooling all resolutions, we divided high resolutions (18-25) from the others.

3. Results

Comparisons of clustering schemes across groups revealed differences which were partly dependent upon the resolution of the clusters: there was little or no differences at low resolutions, but moderate ones at mid and high resolutions (Fig. 2). This suggests that large networks share strong similarities across EBs and SCs. Since it is impossible to verify which resolution is the most representative of FM/Ns, analyses were carried on differences averaged over multiple scales.

To visualize these group differences, we created overlap maps for each atom which belonged to topographically different clusters in each group. These maps show the percentage of time the atom of interest is paired to every other atom in a specific group. Similarly to our statistical tests, the overlap procedure is done across resolutions to yield a single omnibus map per atom of interest. The pattern resulting from the subtraction of two overlap (e.g. EBs-SCs) maps across groups is indicative of the nature of the group differences in topography. For example, a center-surround pattern, where central regions are more likely to be grouped together but less likely to be grouped with the encircling cortices in EBs, would suggest the appearance or strengthening of a module in EBs. Alternatively, if a cluster is less likely to be paired with regions on only one of its sides, its shape is likely to be different (or even smaller) between groups, or it could be more strongly segregated from these cortices.

When results were collapsed across all resolutions, six atoms, three in each hemisphere, were part of topographically different clusters in EBs compared to SCs (Fig. 3a; Table 1). These atom were found within the left fusiform gyrus, middle temporal gyrus and superior occipital gyrus as well as the right inferior occipital gyrus, occipito-temporal sulcus and middle temporal gyrus. Two of the atoms, part of the left superior occipital gyrus and right inferior occipital

gyrus, belonged to clusters encompassing the occipital poles and showed center-surround group differences in their overlap maps. These results suggest the appearance of new modules within EBs occipital pole. The remaining four atoms seemed to evidence stronger segregation between sets of networks (similar to the ventral and dorsal streams, see discussion, Fig. 4 a-f and Fig. 5. a-f).

As can be observed from the consensus and overlap maps, collapsing results across all resolutions yielded statistics which were partly dependent upon large FM/Ns (atoms were paired to physically distant ones). Thus, in order to examine differences in smaller modules, we further investigate the results by carrying the analysis on data collapsed across the highest resolutions only (18-25). Results revealed 4 atoms of interest which we ascribed to topographically different clusters in EBs compared to SCs (Fig. 3b). These included the left middle occipital gyrus, left middle temporal gyrus, and parieto-occipital sulcus, as well as the right middle occipital gyrus. An overlap map was also created for these atoms (Fig. 6 and 7). Again, results evidenced greater segregation between ventral and dorsal regions (Fig. 6 a-f), as well as a novel cluster within EBs right occipital pole (Fig. 7). However, the pattern was slightly different for the left occipital pole its module seemingly invading the calcarine fissure.

4. Discussion

In the current study, we investigated how early visual loss influences the structure of functional modules and networks in the occipital cortex. To quantify topographical differences in FM/Ns between EBs and SCs, individuals from both populations were scanned while their mind was left to wander (resting-state). Each participant's "visual" cortices were subdivided into sets of functionally homogeneous clusters. Comparisons of the cluster's topographies were

made using the Sørensen-Dice coefficient which measured within-group and between-group similarities. These two values were then contrasted to evaluate whether EBs' clusters differed significantly from those of SCs. Collapsed across multiple resolutions (3-25 clusters per hemisphere), our analyses provided results which were unbiased toward modules of large or small sizes. However, due to our interest in topographical differences within small circumscribe modules, we also analyzed the results when solely collapsed across high resolutions (18-25).

The method just described is novel and distinguishes itself from most previous studies on two general points. First, it is holistic and a-priori light. Specifically, it does not rely on pre-existent hypotheses for design or stimulus selection like most task activation studies, nor does it depend on seed selection like functional connectivity studies, and it makes no assumption as to which clustering resolution is most representative of FM/Ns. Second, and crucially, it allows to investigate the exact loci underlying the difference in cluster topographies across groups, and it can identify clusters which are specific to a group. As was seen, our approach was shown to underline novel findings as well as to be in accord with known differences between EBs and SCs evidenced by task-dependent studies.

To briefly summarize our results, both maintenance and modification of the cluster topographies were observed in EBs. Remarkably, we even underline the possible existence of new FM/Ns within EBs occipital poles. Thus, our results promote the view that the establishment of segregated functional modules in occipital regions is partly, but not fully, dependent upon visual experience.

4.1 Maintained functional modules in blindness

Our method allowed us to probe differences in functional topography between EBs and SCs over a large range of cortices usually ascribed to vision (occipital lobes and ventral occipito-temporal lobes). Still, only a limited number of group differences were found, suggesting that the development of FM/Ns is mostly independent of visual experience. Strikingly, low resolutions were marked by an absence of group differences (resolution 3 and 4, Fig. 3), suggesting that large FM/Ns are maintained in EBs.

The observation of restricted difference in the functional clusterization between EBs and SCs is congruent with findings of activation and functional connectivity studies. Evidences of maintained functional units within occipital regions in early or congenital sight-loss agrees with multiple studies which have shown the presence of ventral and dorsal visual pathways in blind individuals (Dormal, Lepore, & Collignon, 2012; Heine et al., 2015) as well as similar retinotopic organization (Striem-Amit et al., 2015). Indeed, various higher “visual” areas tend to retain their general cognitive function (for a review, see Ricciardi et al., 2014) as well as maintaining highly similar functional correlation patterns (Wang et al., 2014). Together, these results are generally taken to mean that higher order visual regions are supramodal in nature (Heimler et al., 2015; Pascual-Leone and Hamilton, 2001; Ricciardi et al., 2014), or, alternatively, that an occipital region can reorient its preferential tuning toward non-visual sensory inputs in blind individuals while maintaining its intrinsic computational abilities (e.g. processing motion; see Dormal et al., 2016), and pattern of connectivity (Collignon et al., 2009; Collignon et al., 2012). Furthermore, the similarity of our results to those of activation and connectivity studies provide strong grounds to the validity of our method.

The limited topographical differences extend even to some FM/Ns found within early “visual” areas, and that have been shown to be implicated in radically different functions in EBs compared to SCs (e.g. language, memory, and braille: Amedi et al., 2003, Cohen et al., 1999; Sadato et al., 1998; Bedny et al., 2011). Combined, these results imply that these higher functions invade specific FM/Ns rather than simply developing into a new module with its own topography. Similarly to higher “visual” areas, these regions might possess specific characteristics that make them suitable for these functions.

4.2 Increased segregation of maintained functional modules

Most of the group differences we observed were not indicative of new FM/Ns in EBs but of increased internetwork segregation. Indeed, new modules would show a center-surround change in topography: stronger pairing with surrounding cortices and weaker pairing with regions enclosing these cortices. However, when results were collapsed across all resolutions, this center surround effect was not present for four out of the six topographical differences between EBs and SCs (Fig. 4). Instead, there seemed to be stronger segregation between two adjacent regions in EBs (Fig.). This effect was also apparent at high resolutions (Fig. 6 a-f).

This increased segregation in EBs is especially clear for two clusters shown to encode auditory motion in blind participants (Dormal et al., 2016), and which bore strong resemblance to area hMT+ (Fig. 5d-f and 6a-c; see Dormal et al., 2016). Usually ascribed to the dorsal visual pathway, these regions showed greater ventro-dorsal segregations in EBs than SCs, a finding that support the observation of diminished functional connectivity between these pathways in EBs (Heine et al., 2015). Interestingly, in vision, cross-talk between hMT+/MST and ventral regions has been hypothesized to link an object to its motion component (for a review, see Perry

and Fallah, 2014). The greater segregation observed here suggests that this influence might be weaker in EBs. If so, why are “visual” regions less involved in this process in EBs even though they individually serve similar functions in SCs? To speculate, EBs might rely on reinforced connectivity between this region and the temporal cortex (Dormal et al., 2016) to link an auditory object to its motion component (Cloutman, 2013).

A second segregation effect was observed for a network composed of the rostral fusiform gyrus and transverse occipital sulcus (Fig. 5a-c; Fig. 6 d-f). These two distant regions formed a more tightly interconnected network in both hemispheres: they were paired together more often while being simultaneously separated from other cortices such as the region resembling hMT+. Highly similar regions have been shown to be involved in place processing; the left fusiform gyrus atom was remarkably close to the central coordinates of the parahippocampal place area (SCs: Epstein et al., 1999, EBs: He et al., 2013; Wolbers et al., 2011) whereas the right transverse occipital sulcus coordinates were highly similar to those of an area involved in scene analysis (SCs: Ganadren, Mullin, & Steeves, 2013; Grill-Spector, 2003). This “scene network” has already been shown to be maintained in EBs (He et al., 2013; Kupers et al., 2010). Our results however suggest that those regions are less reliant upon other occipital networks and/or depend more strongly upon auditory areas in EB.

Together these results of increased segregation of some specific occipital clusters in EBs suggest that some regions rely on highly specialized FM/Ns with decreased cross-talk to other systems in this population. This might result from stronger dependence upon analyses carried within primary and secondary auditory cortices. However, direct investigation of these processes are required to ascertain these hypotheses.

4.3 Modified functional modules in blindness

The most novel and uncanny results of the current experiment is that, despite widespread clustering similarities between EBs and SCs within higher “visual” cortices, early “visual” areas were subjected to a single, yet significant, change. Specifically, we observed functional clusters found within the right and left dorsal occipital poles which presented a center-surround pattern of group differences. In SCs, the clusters tended to be paired with either primary visual cortices or higher visual regions (Fig. 5g-i, 6g-i, and 8a-c). In EBs, the limited extent of these clusters in both ventral, dorsal, lateral, and centro-caudal axis (see Fig. 5g-i and 6g-i) favours one of two interpretations: the clusters are much stronger in EBs, or specific to EBs. Further support for these interpretations comes from results collapsed at high resolutions (18-25). Strikingly, the right occipital pole evidenced the existence of a new or much stronger cluster in EBs (Fig. 8). The trend was slightly different in the left hemisphere with the occipital pole cluster seemingly invading the dorso-caudal calcarine sulcus (Fig. 7g-i). This last result is in line with the changes in V1/V2 border observed in EBs (Striem-Amit et al., 2015).

Compelling clues to as to the role of the occipital poles in EBs come from a recent study of our group that showed these regions’ functional connectivity vary more strongly across time (Pelland et al., 2016). We conclude that EBs’ occipital poles are likely involved in a multitude of temporally distinct but spatially overlapping networks (Smith et al., 2012). This explains the non-specific response of these dorsal occipital poles to a variety of sensory modalities and tasks (Renier et al., 2010). Paired with findings of direct anatomical connections between early visual areas and non-visual (Falchier, Clavagnier, Barone, & Kennedy, 2002; Rockland & Ojima, 2003), and increased excitability of these same regions to non-visual inputs in blind animals

(Izraeli et al., 2002), these results suggest that the new clusters represent modules which develop exclusively in EBS so as to receive auditory and tactile inputs.

5. Conclusion

Our method allowed us to probe for the first time the impact of early visual-loss upon the organization of functional module within the entire occipital lobe. Crucially we demonstrate that the development of functionally homogeneous modules and networks only partly depends upon sensory inputs, an influence which is susceptible to a region's place within the hierarchical organization of "visual" cortices. Higher-order cortices retain their topography, whereas some lower-level ones are highly reorganized. Furthermore, the congruence of our results with known effects of visual-loss upon functional module, and the revelation of new modules in EBs, shows the reliability and advantage of using our novel approach, which is based cluster-based metrics, to probe network differences between populations of interest.

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Table 1. Atoms belonging to different networks in EBs than SCs.

Regions	Coordinates			t-value
	X	Y	Z	
<hr/>				
Omnibus test – all resolutions				
Left fusiform gyrus	-35	-41	-20	6.95
Left middle temporal gyrus	-57	-67	4	5.51
Left superior occipital gyrus	-17	-92	4	5.72
Right inferior occipital gyrus	43	-88	-9	6.95
Right middle occipital gyrus	40	-83	27	5.46
Right middle temporal gyrus	57	-63	7	5.51
Omnibus test – high resolutions				
Left parieto-occipital sulcus	-7	-75	34	5.06
Left middle temporal gyrus	-57	-67	4	5.46
Left middle occipital gyrus	-25	-96	15	5.11
Right middle occipital gyrus	25	-102	6	6.95

Figure captions

Figure 1. Map of atoms found within the “visual” mask. Each color represent one of 204 set of voxels which were semi-randomly grouped together based on proximity and contiguity.

Figure 2. Number of atoms being assigned to clusters with significantly different topographies in EBs compared to SCs ($p < 0.05$, Bonferoni corrected).

Figure 3. Atoms assigned to clusters with significantly different topographies in EBs compared to SCs ($p < 0.05$, Bonferoni corrected). A) Dice scores are averaged across all resolutions (3-25) before performing the group comparisons, yielding results which are present at most resolutions. B) Dice scores are averaged across high resolutions (18-25) before group comparisons, with results representative of local functional module rather than large scale networks.

Figure 4. For the left hemisphere, overlap maps collapsed across all resolutions (3-25). EBs (A,D,G), SCs (C,F,I), and group differences in overlap (B,E,H) are mapped separately. Only maps for atoms of interest, those which were deemed to belong to significantly different cluster in EBs compared to SCs (see Fig 4a), are shown. Overlap maps are calculated by iteratively going through each resolution and participant to find which atoms are part of the same cluster as the atom of interest. Thus, overlap maps represent likelihood that a certain atom will be grouped with the atom of interest.

Figure 5. For the right hemisphere, overlap maps collapsed across all resolutions (3-25). EBs (A,D,G), SCs (C,F,I), and group differences in overlap (B,E,H) are mapped separately. Only maps for atoms of interest, those which were deemed to belong to significantly different cluster in EBs compared to SCs (see Fig 4a), are shown. Overlap maps are calculated by iteratively going through each resolution and participant to find which atoms are part of the same cluster as the atom of interest. Thus, overlap maps represent likelihood that a certain atom will be grouped with the atom of interest.

Figure 6. For the left hemisphere, overlap maps collapsed across high resolutions (18-25). EBs (A,D,G), SCs (C,F,I), and group differences in overlap (B,E,H) are mapped separately. Only maps for atoms of interest, those which were deemed to belong to significantly different cluster in EBs compared to SCs (see Fig 4b), are shown. Overlap maps are calculated by iteratively going through each resolution and participant to find which atoms are part of the same cluster as the atom of interest. Thus, overlap maps represent likelihood that a certain atom will be grouped with the atom of interest.

Figure 7. For the right hemisphere, overlap maps collapsed across high resolutions (18-25). EBs (A), SCs (C), and group differences in overlap (B) are mapped separately. Only the map for an atom of interest, one which was deemed to belong to significantly different cluster in EBs compared to SCs (see Fig 4b), is shown. Overlap maps are calculated by iteratively going through each resolution and participant to find which atoms are part of the same cluster as the atom of interest. Thus, overlap maps represent likelihood that a certain atom will be grouped with the atom of interest.

Figure 1.

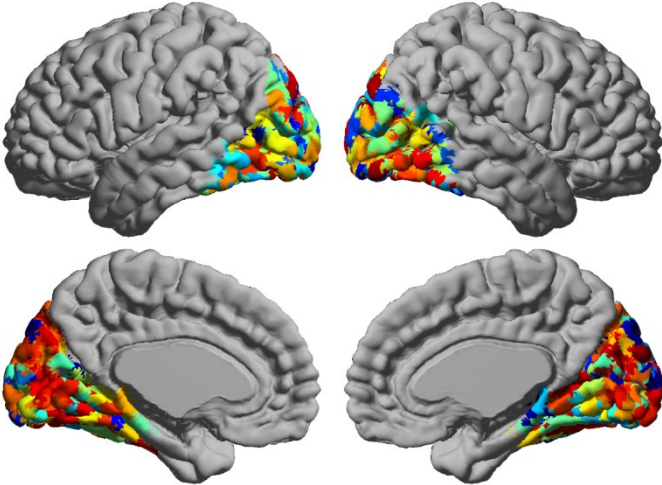


Figure 2.

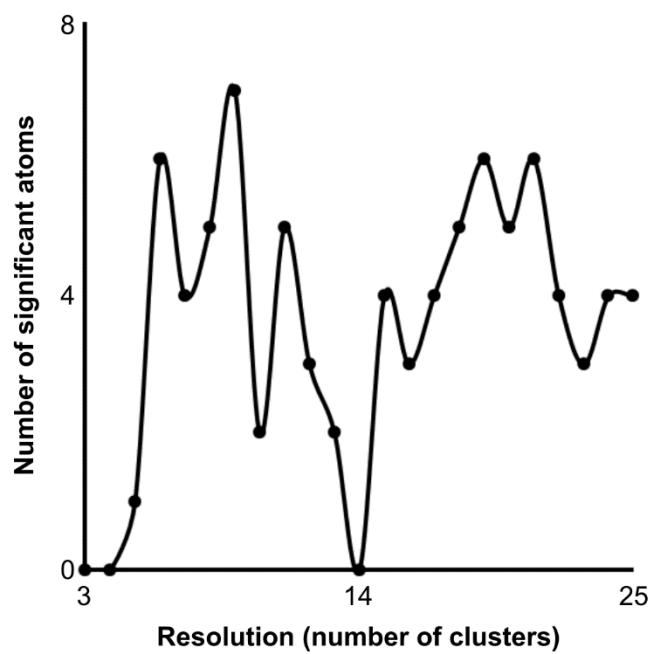


Figure 3.

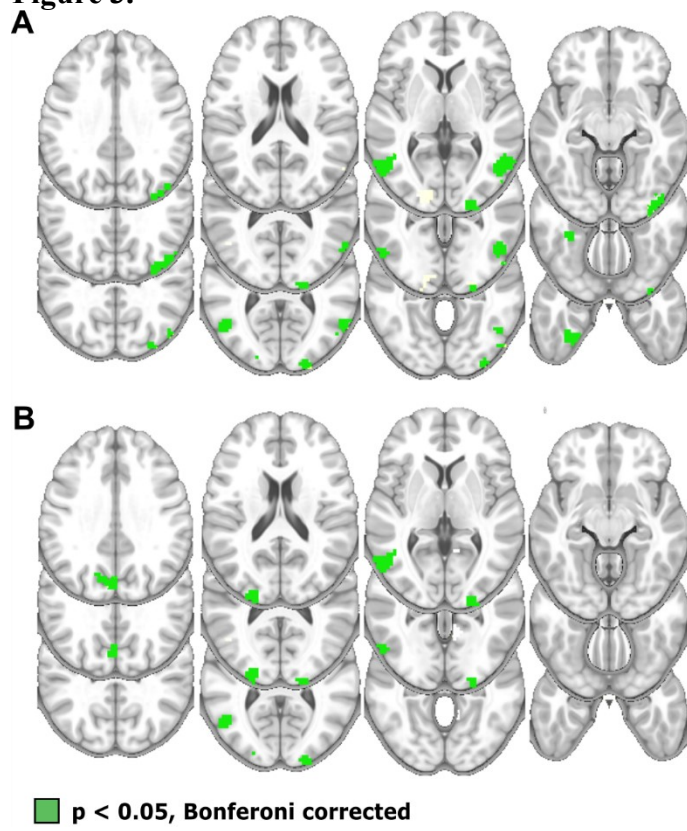


Figure 4

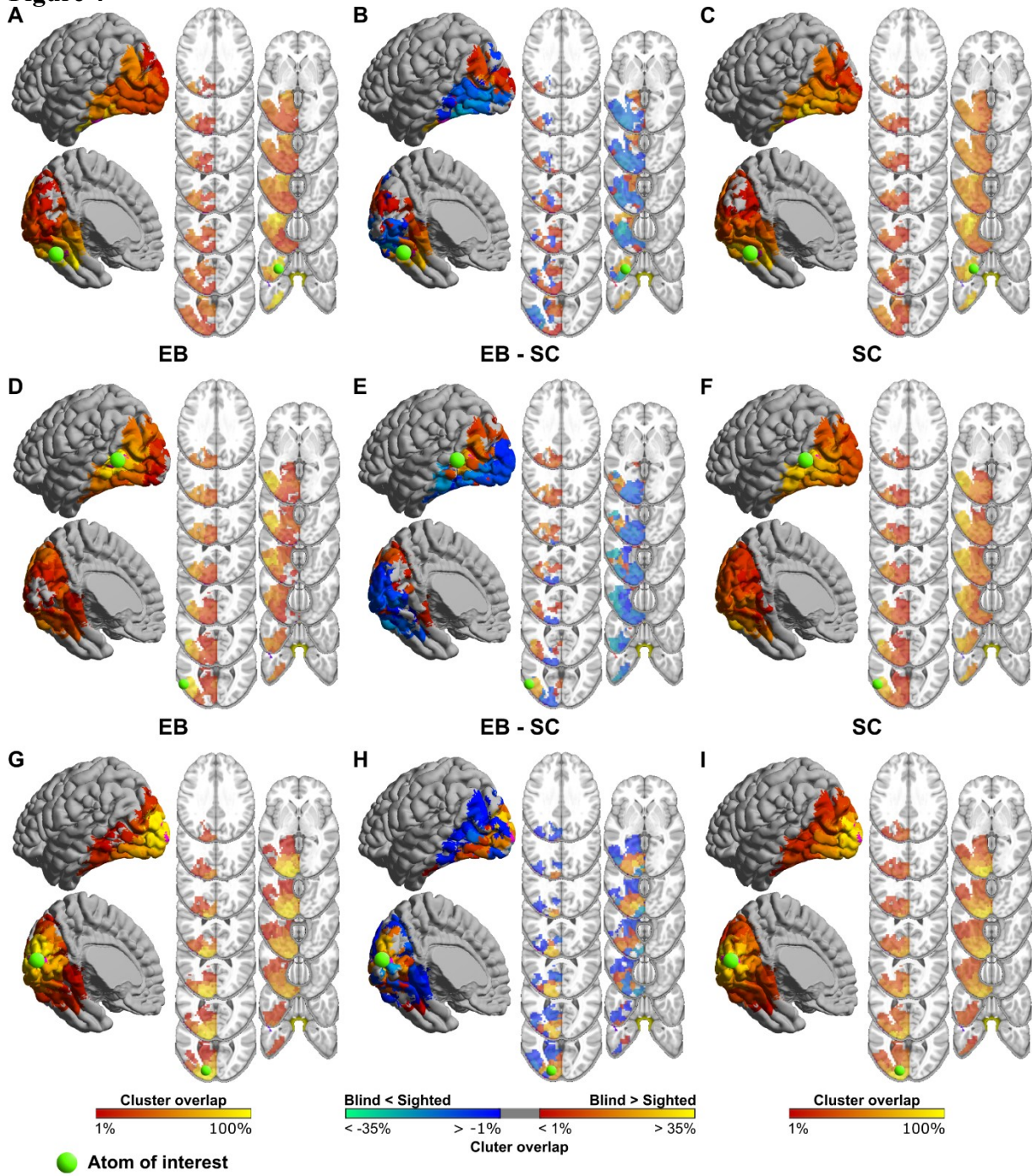


Figure 5.

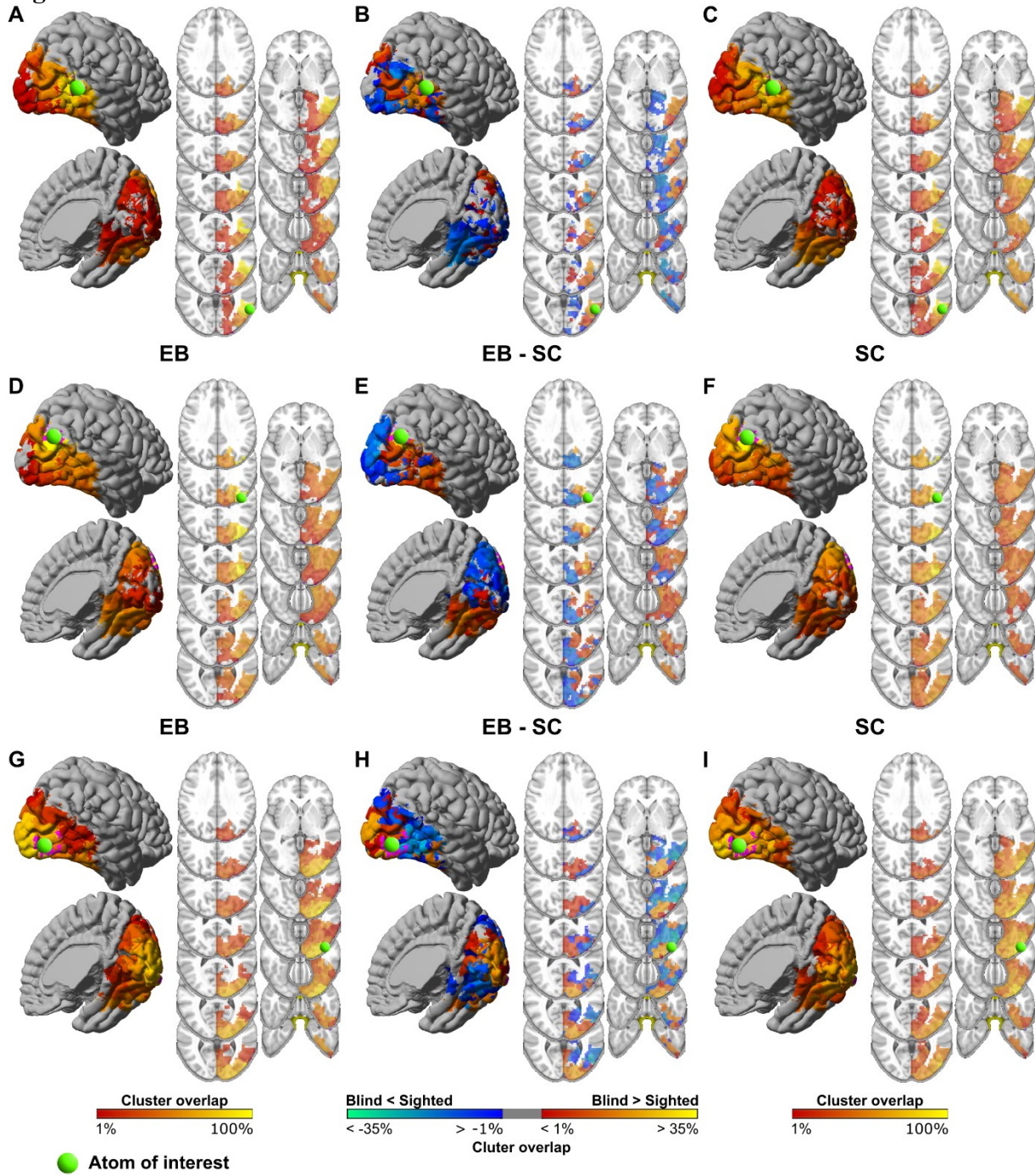


Figure 6.

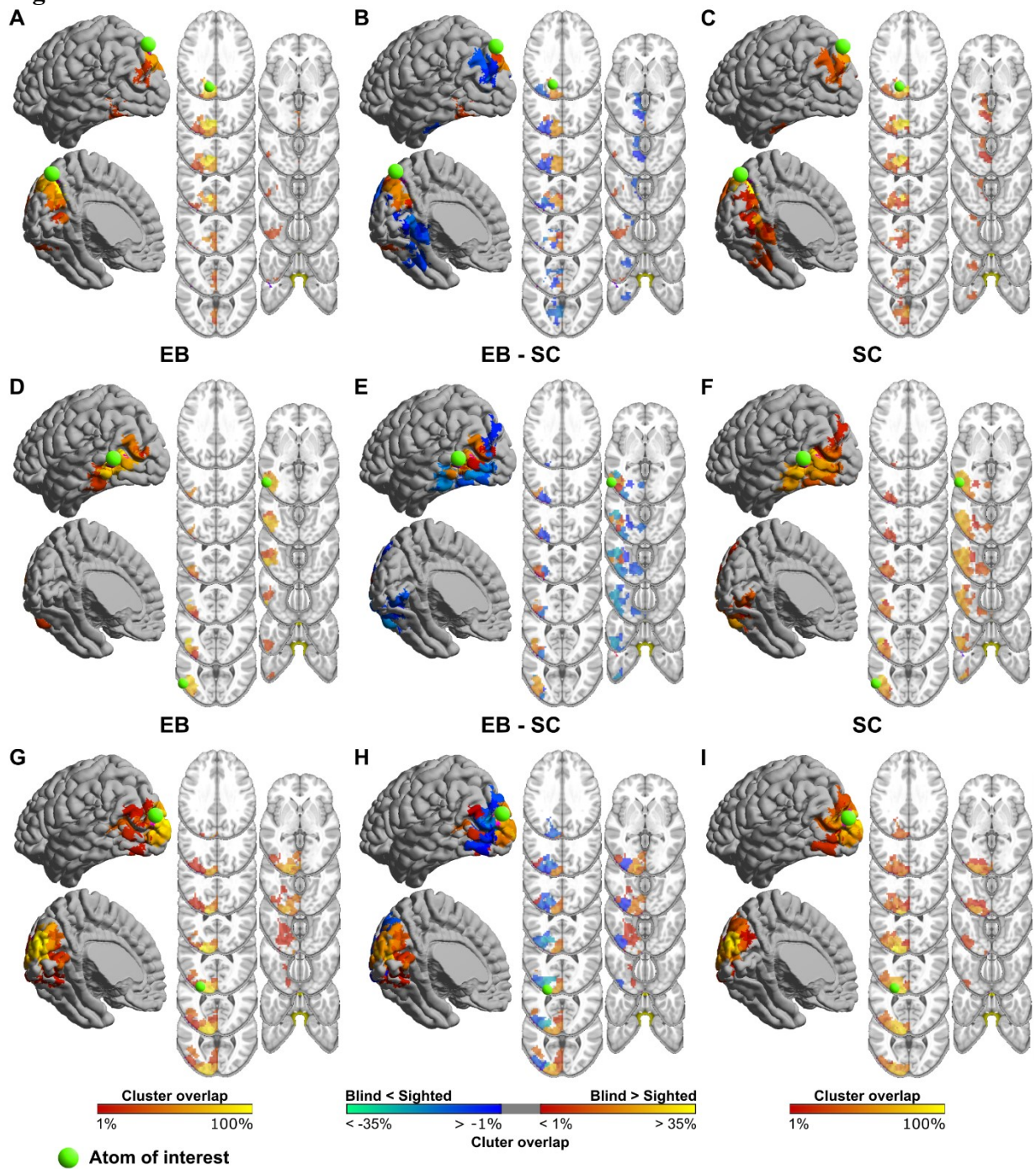
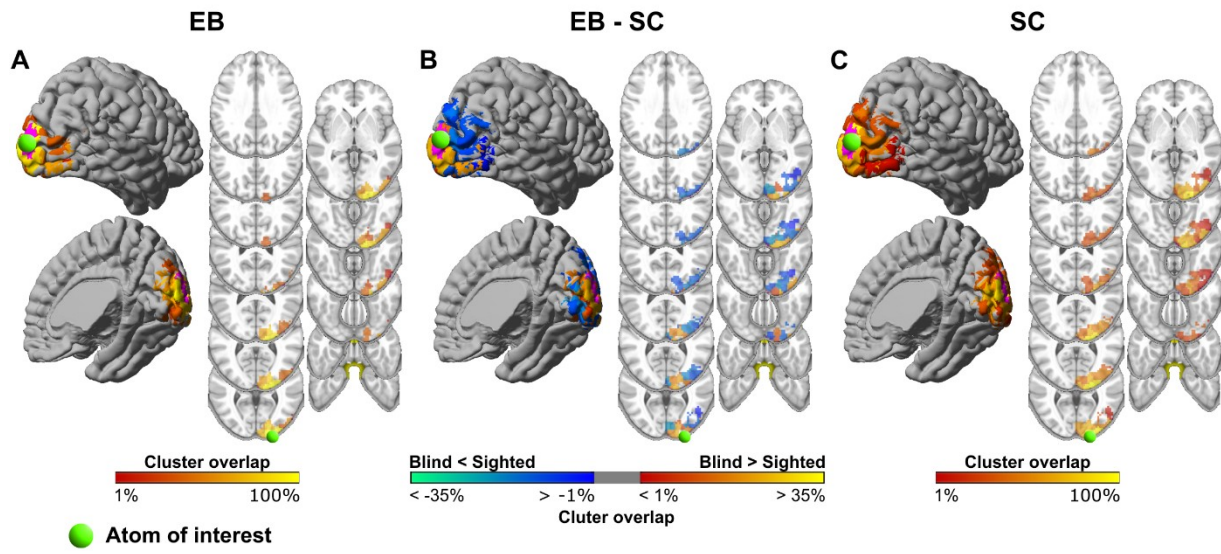


Figure 7.



Supplementary material.

Supplementary tables

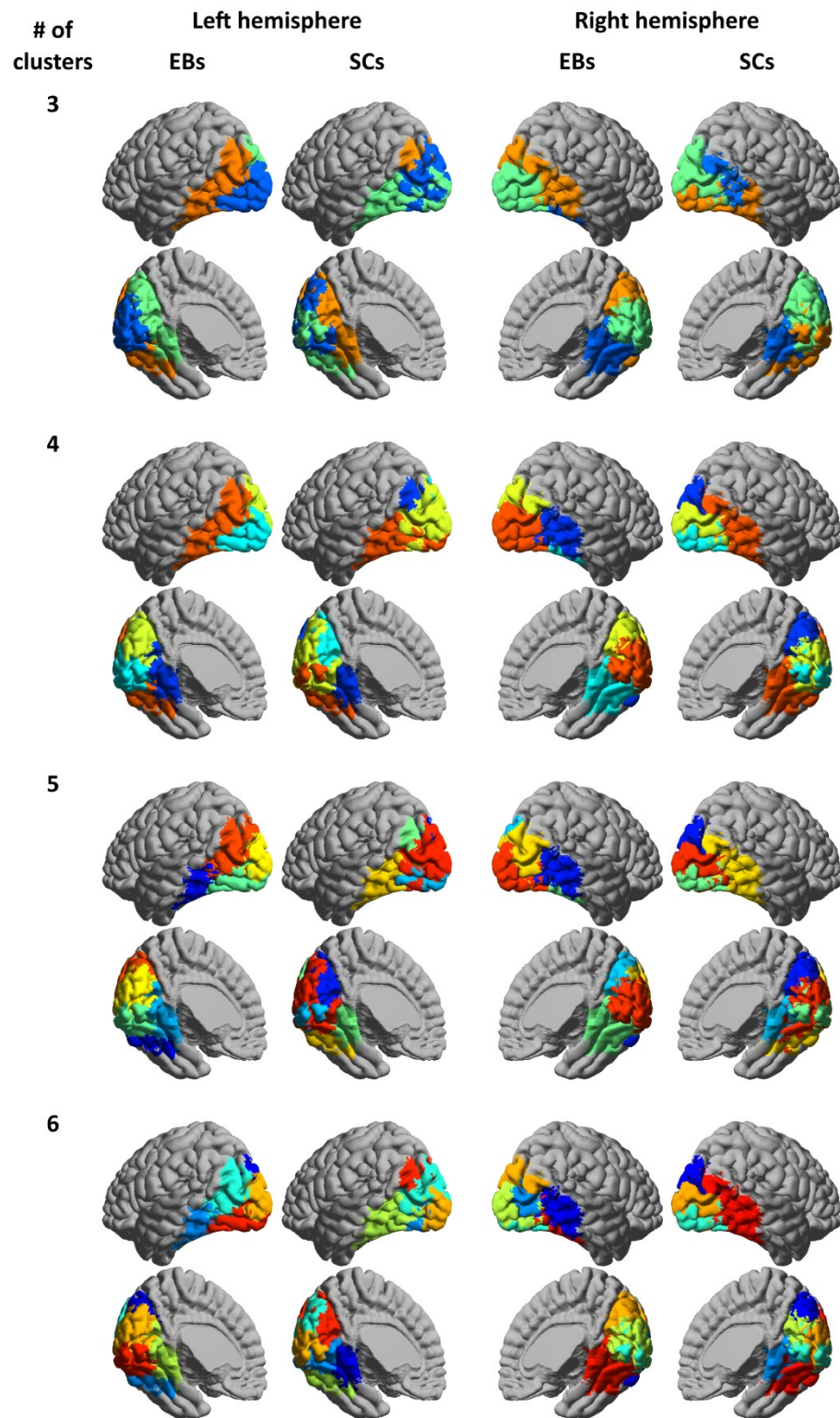
Supplementary table 1. Characteristics of the blind participants.

Participant	Age (y)	Sex	Hand	Residual vision	Onset	Cause of blindness	Education	Musical experience
CB1	40	M	R	No	0	Fibroplasia	University	Yes
CB2	61	M	R	Diffuse light	0	Congenital cataracts	University	Yes
CB3	56	M	R	No	2 months	Electric burn of optic nerve	High school	No
CB4	26	M	R	No	0	Leber's congenital amaurosis	University	Yes
CB5	54	M	R	No	0	Glaucoma	University	Yes
CB6	38	M	R	No	0	Detached retina	High school	Yes
CB7	39	M	R	Diffuse light	0	Leber's congenital amaurosis	University	No
CB8	27	F	A	No	0	Retinopathy of prematurity	High school	No
CB9	56	F	R	No	0	Retinopathy of prematurity	High school	Yes
CB10	32	F	R	No	0	Glaucoma	High school	No
CB11	48	M	R	No	0	Thalidomide	University	Yes
CB12	31	F	R	No	3 years	Retinoblastoma	College	No
CB13	43	M	R	No	0	Glaucoma and aniridia	University	Yes
CB14	46	M	R	No	0	Congenital cataracts and glaucoma	University	Yes

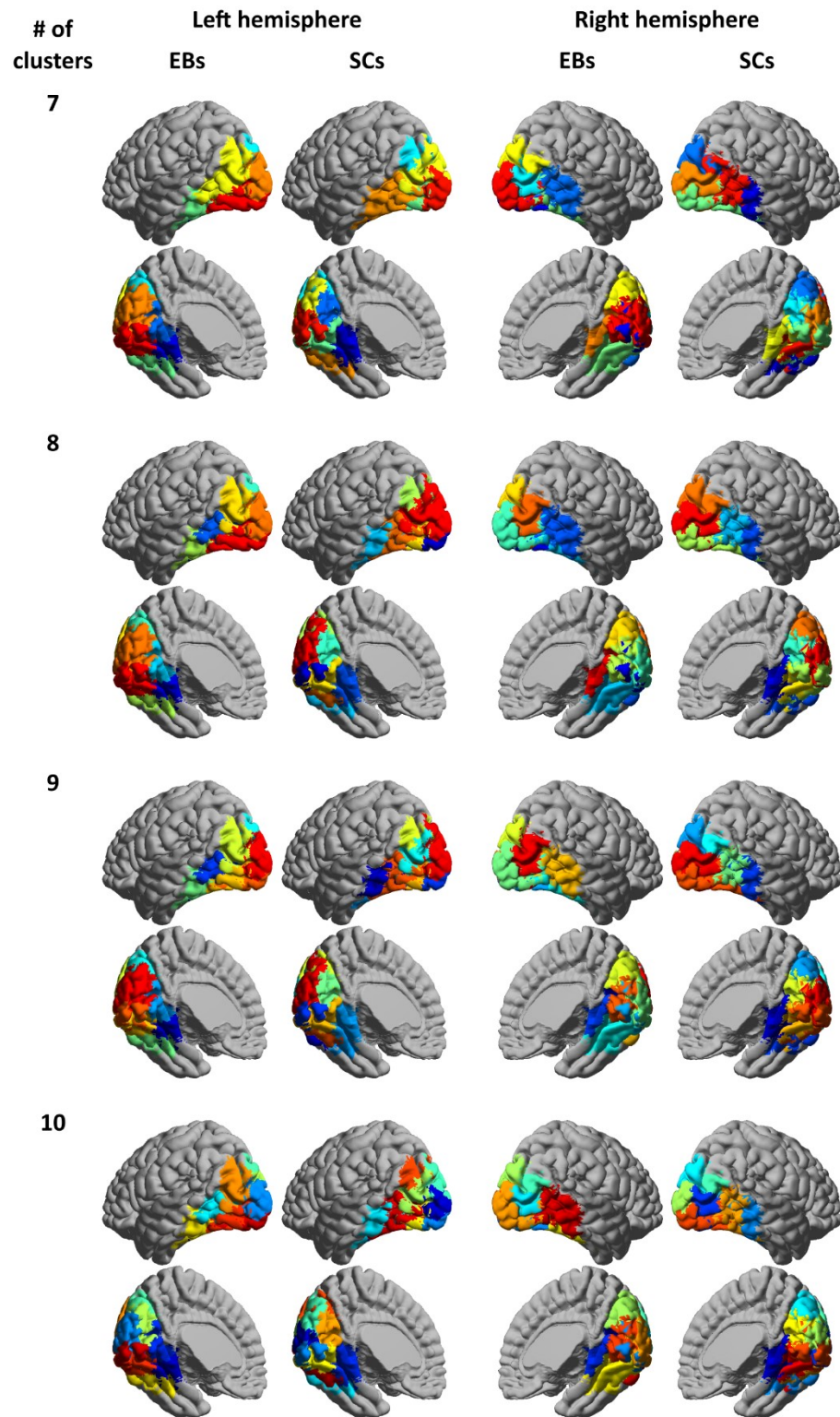
Supplementary figure captions

Supplementary figure 1. Group consensus clusters for the early blind group and sighted group at all measured resolutions. Apparent differences in the clustering scheme should not be taken as statistically significant differences, which are instead presented in figure 3.

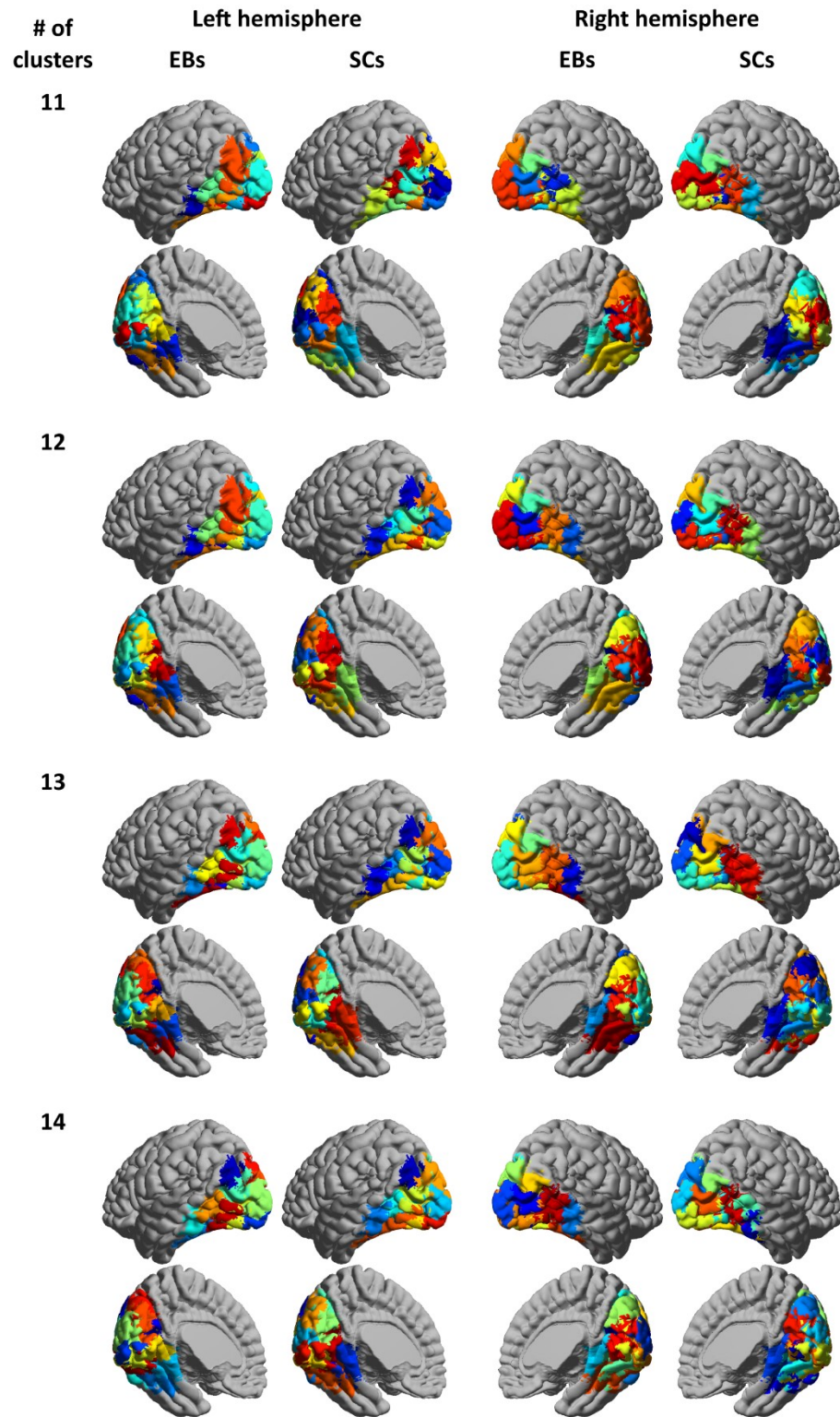
Supplementary figure 1



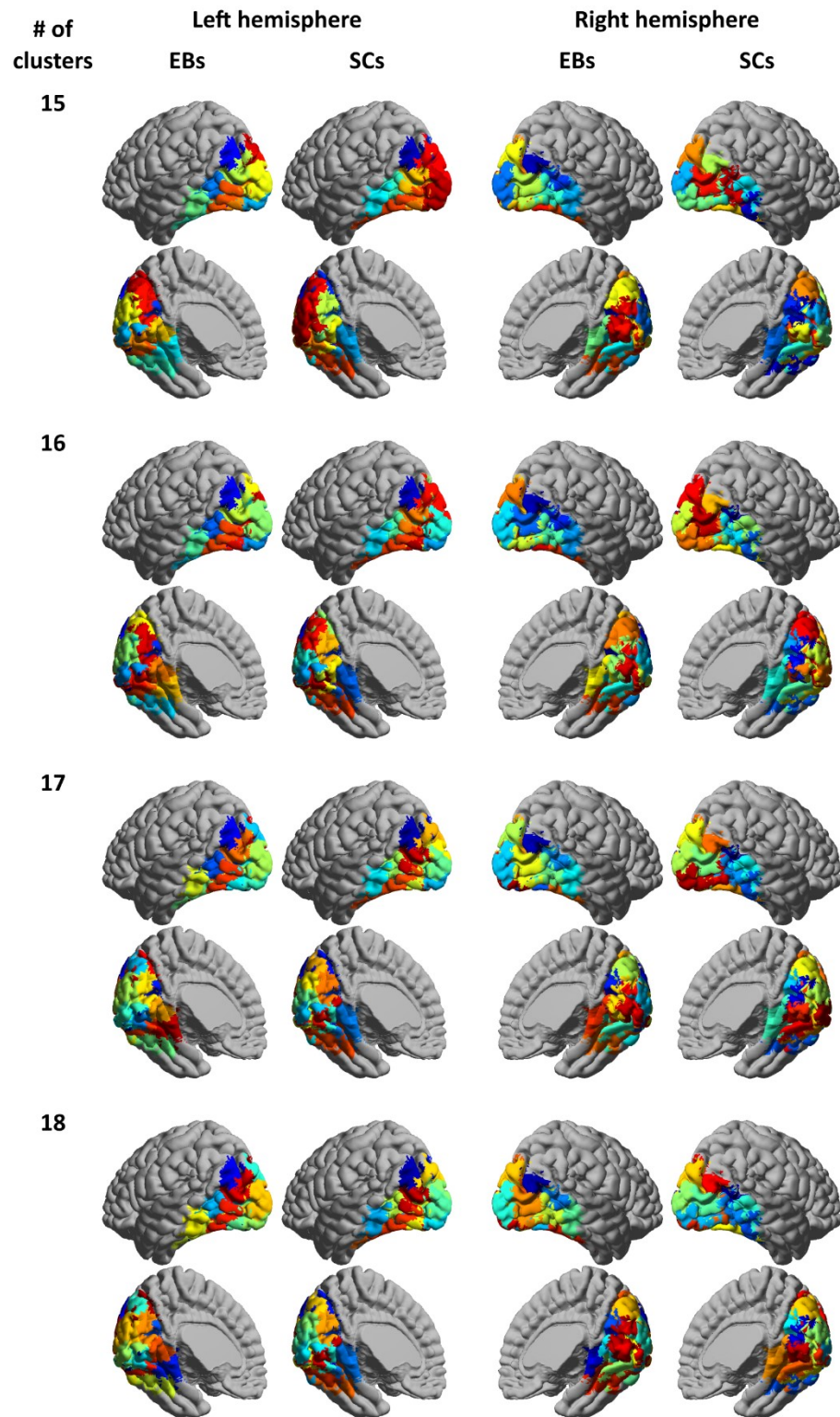
Supplementary figure 1 continued



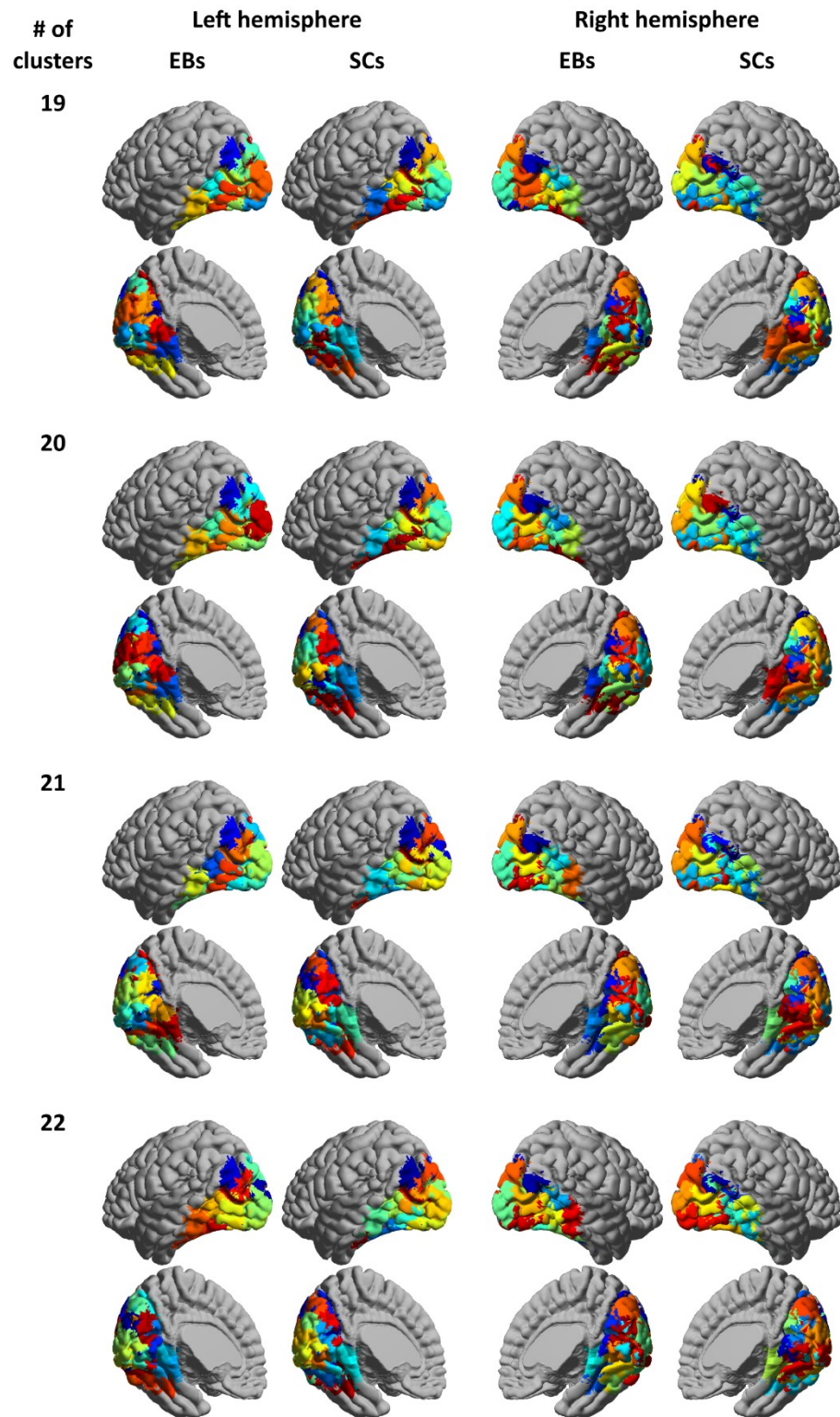
Supplementary figure 1 continued



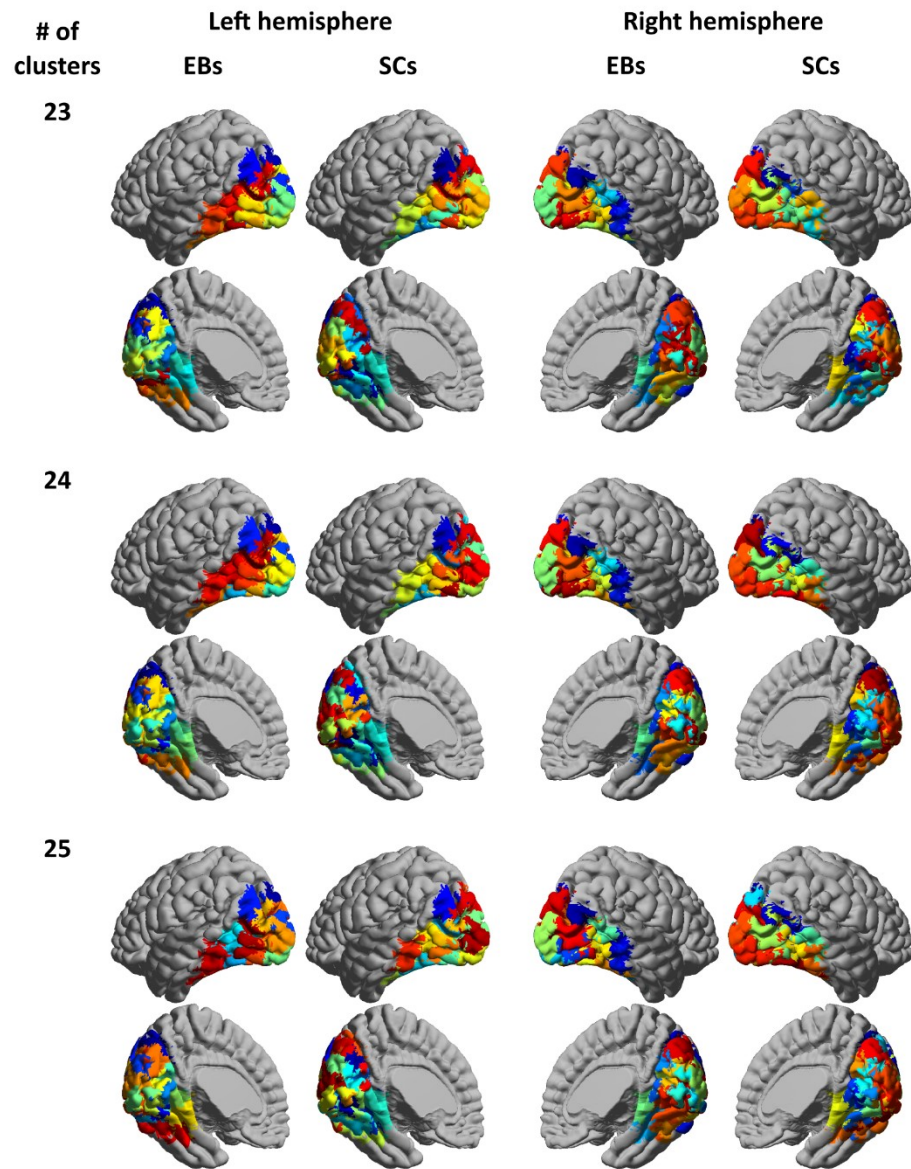
Supplementary figure 1 continued



Supplementary figure 1 continued



Supplementary figure 1 continued



Article #2

Contribution des auteurs

Maxime Pelland: Rédaction de l'article, analyse des données et conceptualisation de l'étude.

Pierre Orban : Conceptualisation de l'étude et analyse des données.

Christian Dansereau : Analyse des données.

Franco Lepore: Conceptualisation de l'étude et financement en tant qu'investigateur principal.

Pierre Bellec: Rédaction de l'article et conceptualisation de l'étude.

Olivier Collignon: Rédaction de l'article, conceptualisation de l'étude, collecte des données et
financement.

State-dependent modulation of functional connectivity in early blind individuals

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Abstract

Resting-state functional connectivity (RSFC) studies have highlighted how visual experience influences the brain's functional architecture. Reduced RSFC coupling between occipital (visual) and temporal (auditory) regions has been reliably observed in early blind individuals (EB) at rest. In contrast, task-dependent activation studies have repeatedly demonstrated enhanced co-activation and connectivity of occipital and temporal regions during auditory processing in EB. To investigate this apparent discrepancy, the functional coupling between temporal and occipital networks at rest was directly compared to that of an auditory task in both EB and sighted controls (SC). Functional brain clusters shared across groups and cognitive states (rest and auditory task) were defined. In EBs, we observed higher occipito-temporal correlations in activity during the task than at rest. The reverse pattern was observed in SC. We also observed higher temporal variability of occipito-temporal RSFC in EB suggesting that occipital regions in this population may play a role of multiple demand system. Our study reveals how the connectivity profile of sighted and early blind people is differentially influenced by their cognitive state, bridging the gap between previous task-dependent and RSFC studies. Our results also highlight how inferring group-differences in functional brain architecture solely based on resting-state acquisition has to be considered with caution.

Highlights

- 1) Occipito-temporal functional connectivity is modified by cognitive states.
- 2) This modulation is different in blind and sighted individuals.
- 3) Blind participants have higher occipito-temporal temporal variability at rest.
- 4) The group difference in variability at rest explains the differences in modulation.
- 5) Inferring group differences with resting-state data should be subject to caution.

Keywords: blindness, cross-modal plasticity, functional connectivity, modulation, resting-state fMRI.

1. Introduction

The study of people deprived of sensory information early in life provides conclusive evidence on how sensory experience shapes the structural and functional architecture of the brain (Frasnelli et al., 2011). Recent researches involving early blind individuals have shed new lights on the old ‘nature versus nurture’ debate regarding brain development: whereas the recruitment of occipital regions by non-visual inputs in the congenitally blind highlights its dependence upon experience to organize itself (nurture’s influence), the observation of specialized cognitive modules in the occipital cortex of congenitally blind, similar to those observed in the sighted, highlights the intrinsic constraints imposed to such plasticity (nature’s influence) (Collignon et al., 2011; Dormal and Collignon, 2011; Reich et al., 2012; Ricciardi et al., 2014).

Gaining deeper insights into how occipital regions in early blind individuals (EBs) are reorganized to support sensorimotor and cognitive functions not only requires studying their response properties (functional specialization), but also understanding how they are integrated into brain networks (functional integration) (Friston 2003). An increasingly popular approach to study short and long-range brain interactions is to measure functional connectivity (FC) during a resting-state (RS; van den Heuvel and Hulsoff Pol, 2010). With resting-state functional connectivity (RSFC), spontaneous fluctuations in functional magnetic resonance imaging (fMRI) signal, observed while participants are resting, are correlated to infer FC between intrinsically connected brain regions (Biswal et al., 1995). Therefore, RSFC is a measure of temporal synchrony of fMRI signal between distinct brain regions (Friston et al. 1993). Since functional networks have distinct temporal characteristics, separate functional networks can be identified from a single time series of resting fMRI data (Beckmann et al. 2005).

Research on the effect of early visual deprivations using RSFC protocols has evidenced both enhanced segregation (i.e. decreased connectivity) and integration (i.e. increased connectivity) of occipital regions (see Bock and Fine, 2014 for review). A striking and often replicated result emerging from those studies is the reduced connectivity of EBs' occipital regions with primary somatosensory and auditory areas (Bedny et al., 2011; Burton et al., 2014; Liu et al., 2007; Yu et al., 2008; Striem-Amit et al., 2015; see Bock and Fine, 2014 for a recent review). This reliable effect at rest contrasts with the large amount of studies reporting enhanced task-dependent activations of occipital regions during the processing of auditory and tactile inputs (see Bavelier and Neville, 2002; Frasnelli et al., 2011 for review) in EBs. Importantly, the functional relevance of occipital activity to EB's non-visual sensory/perceptual processing is supported by studies showing reduced performance to specific tactile and auditory tasks following the disruption of EB's occipital cortex through the application of transcranial magnetic stimulation (TMS) (Cohen et al., 1997; Collignon et al., 2007, 2009). Moreover, TMS directly applied over the occipital cortex can elicit paresthesiae in the fingers of early blind braille readers (Cohen et al. 1997; Ptito et al., 2008). Further support comes from studies of effective connectivity (causal connectivity; Friston 1994) estimated by dynamic causal modelling of fMRI data (Friston 2003) or by combining TMS with Positron Emission Tomography (PET) (measuring activity induced by magnetically exciting distant cortical regions), which have shown stronger coupling between auditory or somatosensory areas and occipital regions in EBs than in SCs (fMRI: Collignon et al., 2013; Klinge et al., 2010, PET and TMS: Wittenberg et al., 2004). Finally, the participation of occipital cortex in non-visual processes early in time following stimuli presentation (Collignon et al., 2009; Leclerc et al.,

2000; Röder et al., 1999) suggests the existence of direct links between occipital and other non-visual sensory regions.

We suggest that this apparent inconsistency between RSFC and task-dependent studies originates from the presupposition that RS networks are good proxies for networks instantiated during cognitive/perceptual processing (Andric and Hasson, 2015). Even though group level RSFC pattern have been documented to be similar to task co-activation patterns (Cordes et al., 2000; Smith et al., 2009; Wig et al., 2014), recent work has shown that whole-brain FC networks can be fundamentally reshaped by experience (e.g. Gordon et al., 2014; Orban et al., 2015; Lewis et al., 2009; Tambini et al., 2010), and over short periods of time (Allen et al., 2012; Hutchison et al., 2013b), that they are not constrained by RS topologies, and that this holds particularly true for connectivity structures of sensory systems (e.g. Andric and Hasson 2015; Mennes et al., 2013). Furthermore, investigations of the effect of task-focused attention versus rest/mind wandering in sighted individuals have shown functional coupling across brain regions to be state-dependent (Hampson et al., 2002; Hampson et al., 2004; Jiang et al., 2004; Newton et al., 2007). Specifically, functionally relevant connections show increased connectivity whereas irrelevant connections are decreased during task as compared to rest (Bartels and Zeki, 2005; Nir et al., 2006), with the resulting patterns of FC being specific enough to reliably predict participants' cognitive states (Shirer et al., 2012). Furthermore, evidence that differences in FC pattern between populations can be task-dependent (Çetin et al., 2014; Nair et al., 2014) compellingly illustrates how inferring differences in functional integration between groups solely based on RSFC should be subject to caution.

What is RSFC representative of then? The current view is that the wandering mind sequentially explores multiple functional modes, each with a unique pattern of connectivity, and

sustaining a different function (Deco, Jirsa, & McIntosh, 2011; Karahanoglu et al., 2013). Consequently, a connection's strength will vary as a function of time (see Hutchison et al. 2013a,b), with more temporally variable connections being members of a larger set of modes (Allen et al., 2012). A secondary result of this dynamic nature is that connections measured over a whole run will be representative of no single functional mode, but of their average (Hutchison et al., 2013b, Smith et al., 2012). Of note, if a mode were to be less prevalent in a group, or in competition with a greater number of modes, its connectivity pattern would be more strongly diluted when computed over a whole run, and may consequently appear weaker.

Therefore, the goal of the current study was twofold. First, to investigate how cognitive states, rest and an auditory sensory/perceptual task, would impact FC between occipital and sensory cortices in both EBs and SCs. Second, to verify whether difference in RSFC between EBs and SCs is caused by their membership to a greater number of functional modes in the blind group. To investigate the topic of cognitive state, an auditory task was chosen because occipito-temporal RSFC has been reliably demonstrated to be lower in EBs than in SCs (Bedny et al., 2011; Burton et al., 2014; Liu et al., 2007; Striem-Amit et al., 2015; Yu et al., 2008), and because auditory processing elicits strong responses in both the occipital and temporal cortices of EBs (Collignon et al. 2011; 2013). Thus, participants underwent two fMRI runs, a RS one, and one where they were involved in a challenging auditory task. FC was extracted for each run and population, then the presence of an interaction between cognitive state and groups was tested. Additionally, for the RS run, a connection's variability was measured as a function of time and the resulting metrics compared across groups. Biases caused by a priori definition of regions of interest (Zalesky et al. 2010; Park et al., 2013) were avoided by grouping voxels into functionally homogeneous regions. The actual method used, Bootstrap Analysis of Stable

Clusters (Bellec et al., 2010), has recently been shown to perform well compare to other methods when it comes to subdividing the brain into meaningful functional regions (Ryali et al., 2015).

Based on studies revealing an increase in FC between functionally related areas and a decrease between functionally unrelated areas during tasks (Bartels and Zeki, 2005; Nir et al., 2006), our hypothesis was that the FC between auditory and occipital regions would be differently modulated by the cognitive states in EBs and SCs. Additionally, if some of EBs' occipital regions do participate in a greater number of modes, their specific connections with auditory areas should be more variable than in SCs.

2 Materials and Methods

2.1 Participants

The data of fourteen EBs [4 females, age range 27 - 61 (mean \pm SD, 42 \pm 11)] and 16 SCs [7 females, age range 23 - 60 (mean \pm SD, 39 \pm 14)] were included in the analyses (see supplementary table 1 for more information on blind participants). Student's t-test did not reveal any statistical age differences between groups. One additional SC participated in the study but was excluded from the analyses due to excessive motion during scanning acquisition (see below). Both groups were blindfolded throughout the fMRI acquisition. None of the EBs had ever had functional vision allowing pattern recognition or visually guided behaviour. At the moment of testing, all EBs were totally blind except for two who had only rudimentary sensitivity for brightness with no pattern vision. In all cases, blindness was attributed to peripheral deficits with no neurological impairment. For all subjects, pure-tone detection thresholds at octave frequencies ranging from 250 to 8,000 kHz were within normal limits in both ears. All of the procedures were approved by the research ethic and scientific boards of the Centre for

Interdisciplinary Research in Rehabilitation of Greater Montreal and the Quebec Bio-Imaging Network. Experiments were undertaken with the understanding and written consent of each subject.

2.2 Experimental design

Participants underwent two functional runs. A RS acquisition was carried first in order to avoid task contamination of RS brain activity. This run lasted 5 minutes (136 volumes) during which participants were instructed to relax, not to think about anything in particular, and to keep their eyes closed.

The second run consisted of a 14 minutes long sound discrimination task (400 volumes; 278 acquired when participants are engaged the task) the method, behavioral results, and activation of which have already been described (Collignon et al. 2011; 2013). To summarize, the task run contained 30 blocks (20.4 s duration each) separated by rest periods. Participants had to process the spatial or pitch attributes of the sounds using a staircase method in order to keep correct responses at ~85% which allowed to equalize the difficulty level across tasks and participants. Since our goal was to assess the connectivity between auditory and visual regions independently of the specifics of the task, FC was equally based on data from the spatial and pitch blocks. The use of a staircase procedure inside the scanner notably allowed us to guarantee that the change in connectivity profile between groups is not due to the perceived difficulty level of the task.

2.3 FMRI data acquisition

Functional time series were acquired using a 3-T TRIO TIM system (Siemens) equipped with a 12-channel head coil. Multislice T2*-weighted fMRI images were obtained with a gradient echo-planar sequence using axial slice orientation [time to repetition (TR) 2,200 ms; time to echo (TE) 30 ms; functional anisotropy (FA) 90°; 35 transverse slices; 3.2-mm slice thickness; 0.8-mm interslices gap; field of view (FoV) 192 × 192 mm²; matrix size 64 × 64 × 35; voxel size 3 × 3 × 3.2 mm³]. A structural T1-weighted 3D magnetization prepared rapid gradient echo sequence (voxel size 1 × 1 × 1.2 mm³; matrix size 240 × 256; TR 2,300 ms; TE 2.91 ms; TI 900 ms; FoV 256; 160 slices) was also acquired for all subjects.

2.4 FMRI data preprocessing

The datasets were analyzed using the NeuroImaging Analysis Kit (NIAK_0.7c3; <http://niak.simexp-lab.org>) (Bellec et al., 2012), under CentOS with Octave (v3.6.2; <http://gnu.octave.org>) and the Minc toolkit (v0.3.18-20130531; <http://www.bic.mni.mcgill.ca/ServicesSoftware/ServicesSoftwareMincToolKit>). All analyses were executed in parallel on the "Mammouth" supercomputer (<http://www.rqchp.ca/fr/access-aux-ressources/serveurs/mp2>), using the pipeline system for Octave and Matlab (PSOM 1.0) (Bellec et al., 2012).

Each fMRI run was corrected for inter-slice differences in acquisition time and rigid body motion. Then, the mean motion-corrected volume of functional data was coregistered with the T1 individual scan, which was itself non-linearly transformed to the Montreal Neurological Institute (MNI) non-linear symmetric template (Fonov et al., 2009; Fonov et al., 2011). Functional volumes were resampled to MNI space at a 3mm isotropic resolution. To minimize artifacts due to excessive motion, some time frames were removed (see method below).

Afterward, slow time drifts (high-pass filter with a 0.01 Hz cut-off), the average signals in conservative masks of the white matter and the lateral ventricles, and the first principal components (95% energy) of six rigid-body motion parameters and their squares were regressed out of the time series. Finally, the volumes were spatially smoothed with a 6mm Gaussian kernel.

Absolute head motion parameters were compared between groups for both the task and RS datasets. No significant differences were found, neither between conditions and groups, nor for their interaction. To further rule out the possibility that the observed functional connectivity variability could be accounted for by inter-subject differences in head motion, the scrubbing method of Power et al. (2012) was used to remove volumes with excessive motion (frame displacement greater than 0.5 mm). A minimum number of 80 unscrubbed volumes per run, corresponding to 176s of acquisition, was then required for further analysis. For this reason, data from one SC were removed from the sample.

2.5 Functional brain clustering

The method developed by Bellec and colleagues (Bellec et al., 2010), called multi-level Bootstrap Analysis of Stable Clusters (BASC), was used to separate the brain into functional clusters for the connectivity analysis. These clusters each defined a circumscribed network or cerebral region. The choice for using BASC to obtain clusters was done with two goals in mind. First, it groups voxels into functionally homogeneous clusters across participants, a criteria usually not achieved through anatomical parcellation of the brain, and shown to affect FC results (Park et al., 2013). Second, the clustering solution of the method is representative of each group and condition since it is based on every functional time series that were recorded for this

experiment Of note, consensus-based clustering such as BASC have been found to reliably identify functional subdivisions in a variety of brain areas with good biological plausibility and agreement with other imaging modalities (Ryali et al., 2015)..

The first step of the analysis was to reduce the computational burden of the subsequent cluster analysis by deriving ~1,000 regions. To this end, a region-growing algorithm was applied on the voxelwise fMRI time series obtained from the concatenation of the rest and task runs (Bellec et al. 2006). These regions, called atoms, exclusively covered the grey matter and had a controlled size of 1000 mm³. Then, a cluster analysis was applied on the averaged fMRI time series of each atom to identify brain networks that consistently exhibited similar fluctuations between the rest and task runs in individual subjects.

At the group level, BASC quantifies the reproducibility of a cluster analysis, while providing a clustering solution that captures the most stable features across many bootstrap samples. To ascertain that the resulting clustering solutions would be equally representative of both groups (EBs; SCs) and cognitive states (rest; task), a stratified bootstrap sampling method, which creates samples that are balanced with respect to these factors, was implemented. Thus, functional clusters for this study were defined by consensus clusters, which were composed of regions with a high average probability of being assigned to a certain cluster in both groups and cognitive states. We generated a group-level consensus resolution of 50 clusters (see Fig. 1C) since this resolution provides an optimal trade-off between decreased sensitivity due to correction for multiple comparisons versus anatomical precision (Bellec et al., 2015). The center coordinates and average size of each cluster can be found in supplementary table 2 (see Fig. 2 for the clustering scheme).

2.6 Occipito-temporal connectivity analysis

Based on our a priori hypothesis and the use of an auditory task, we focused our analyses to connections of interest (COI) between temporal ('auditory') and occipital ('visual') clusters. After separating the brain into 50 clusters, the auditory temporal cortex was limited to 1 bilateral cluster and the occipital cortex to 7 clusters (see Fig. 2C,D). Decisions as to which cluster should be considered part of the visual cortex was based on two criteria: 1) the most dorsal clusters were roughly limited by the parieto-occipital fissure, and 2) the most ventral clusters included the posterior fusiform gyri and the lingual gyri. Such liberal criteria were selected in order to include visual areas that are subject to neuroplastic changes following early blindness as indexed by unusual RS characteristics (Liu et al., 2007; Liu et al., 2011; Burton et al., 2014) or functional reorganization following early visual deprivation (Collignon et al., 2011; Gougoux et al., 2005; 2009; Hölig et al., 2014).

Our connectivity analysis followed a 2 x 2 factorial design (groups x cognitive states), and was carried twice. In the first iteration, FC at rest was compared to FC during the task, the latter one being computed from time series which had had sustained task-evoked activity modeled out. In the second iteration, FC at rest was compared to FC during the task, but with the raw preprocessed time series. However, similarities between co-activations resulting from block designs and clusters linked by high FC (Cordes et al., 2000; Di et al., 2013; Laird et al., 2013; Smith et al., 2009; Wig et al., 2014) suggests that, for the task dataset, results obtained from raw preprocessed time series might be redundant with those provided by activation studies (Debas et al. 2015). Thus, removing task-evoked sustained activity was necessary to avoid any FC effects which might arise from the blocked design of the auditory task (Fair et al. 2007; Nair et al., 2014) and provide results which are original. Regressing out task-evoked activity from

time series was done by modeling task-related BOLD effects using a boxcar function that was convolved with the canonical hemodynamic function. Task-induced variance was removed from time series using the general linear model. The resulting residuals were used as surrogate time series for the computation of the auditory task FC.

Inter-cluster connectivity between every occipital clusters ($n=7$) and the temporal one (a single bilateral cluster) was defined as the Fisher transform of the Pearson correlation coefficient of the average time series of each cluster. The Fisher transform was implemented so that correlation coefficients would follow a Gaussian distribution (see Bellec et al., 2006). Of note, when cluster encompassed the two cerebral hemispheres, then its functional connectivity measure was based on the BOLD signal averaged across the two hemispheres. Since we were interested in comparing how FC is modified by the cognitive state in EBs and SCs, we then computed the modulation effect (which we define as the difference of FC between the two cognitive states: task FC - rest FC) for each connection and participant.

A random-effect group-level general linear model was estimated for the modulation effect of all COIs. Blindness, intercept, age, sex and motion, were entered as covariates with the later four being confounding variables. This allowed to test the presence of a main effect of groups (EB and SC) and to investigate whether some connections showed a stronger effect than others between groups (interaction of connections \times groups). Effects of this omnibus test were considered significant for $p < 0.05$. Post-hoc tests were carried on single connections using the same general linear model as above. A false discovery rate (FDR) procedure (Benjamini and Hochberg 1995) was implemented to correct for the multiple comparisons arising from post-hoc tests. Threshold of statistical significance was set at $q < 0.05$. Finally, since the intra-subject FC between any two connections was not significantly correlated in either the RS or task-state

(Bonferonni or FDR corrected), no corrections were made for data dependency.

2.7 Functional connectivity variability analysis

A sliding window analysis was used to measure this variation over time. Since the removal of time frames by the scrubbing procedure would affect the temporal nature of the analysis, data were reprocessed using the same parameters as above but forgoing the scrubbing step. In order to still maximally control the effect of motion on FC, frame displacement (FD; Power et al., 2012) values were used as covariates during statistical analysis. Instead of using the full run, data from windows of 21 TRs (46.2 s) were employed. They were slid in steps of 1 TR resulting in a total of 116 windows per participant for the RS (similar to Allen et al., 2012, and considered to be optimal: Hendriks et al., 2016). Pearson's correlation coefficient between the time series of occipital and temporal clusters was computed for each window and then Fischer transformed. A functional connection's variability across time was defined as the standard deviation of the aforementioned Fisher transformed correlation across time windows.

If some of EBs' occipital regions do participate in a greater number of modes, their specific connections with auditory areas should be more variable than in SCs. This prediction was tested for connections of the COI analysis which had been found to have a different modulation effect in EBs than SCs. Each connection was individually tested using the GLM to control for variables of non-interest (age, sex, FD). Considering that only strong FC variability can be detected using fMRI runs as short as 5 minutes (Hindriks et al. 2015), any group differences unveiled by this analysis should be reliable.

To further investigate whether there exists a relationship between group differences in the modulation effects and group differences in a connection's variability, we computed the

average value of those variables for each occipito-temporal functional connections and correlated them. Our hypothesis was that connections showing a stronger modulation effect in EBs than SCs did so because they were involved in a larger number of networks and, hence, should be more temporally variable at rest in EBs.

3. Results

3.1 Occipito-temporal connectivity

As mentioned above, the COI analysis comparing the modulation effect across groups [EBs(task - rest) vs SCs(task - rest)] was run twice, once with surrogate time series from which the effect of the block design were removed, and once with raw preprocessed time series. Whether or not the effect of block was modeled out of the time series did not strongly affect FC values (see Supplementary table 3). Thus, only results for the tests carried on the time series from which task activations were modelled out are reported below.

An omnibus test [2 (groups) x 7 (connections) ANCOVA] showed no main effect of group ($p < 0.11$), but the interaction effect was significant ($p < 0.001$, Huynh-Feldt corrected) (Fig. 3), meaning that this effect was stronger for some connections than others. Post-hoc tests revealed two connections for which the between-group difference in modulation effect survived the FDR correction (Fig. 3 and 4). These connections involved the temporal region and the middle occipital gyrus (mostly the left hemisphere, #37) and the superior occipital gyrus (mostly the right hemisphere, # 47).

3.2 Functional connectivity variability

Functional connections showing a distinct between-group modulation effect in the COI analysis also tended to be more variable across time in EBs, with the middle occipital gyrus being significantly more variable in EBs ($p < 0.05$) and the superior occipital gyrus showing a similar albeit non-significant trend (Fig. 5, see Supplementary Fig. 1 for all seven occipito-temporal connections). Moreover, a relationship between group differences in the modulation effect (EBs[task - rest] – SCs[task - rest]) and FC variability (EBs - SCs) is also supported by the highly significant correlation between these variables ($r(6) = 0.9685$, $p < 0.001$), with occipito-temporal connections showing stronger modulation effect in EBs also showing higher variability in EBs (Fig. 6). This high correlation cannot be taken as a mathematical artifact since it was specific to occipito-temporal connections but did not hold for the remainder of the brain's FC (Fig. 6; $r(1196) = -0.041$, $p = 0.16$).

4. Discussion

In order to study how alterations of occipito-temporal connectivity due to early visual deprivation are influenced by cognitive state, EBs and SCs were scanned during rest and while involved in a demanding auditory task. Unbiased functional regions common across tasks and groups were defined (Bellec et al., 2010), and correlations between the region's time series served as an index of FC which was compared across groups and cognitive states. We observed that occipito-temporal connectivity was lower during rest than during the auditory task in EBs, whereas the reverse pattern was observed in SCs (see Fig. 3). Our finding of an interaction effect between cognitive states and groups on FC is consistent with a body of recent studies showing how specific contexts of information processing fundamentally impact the strength of FC

between brain regions (Eckert et al., 2008; Hasson et al., 2009; Moussa et al., 2011). For this reason, population differences in static RS networks metrics should not be considered to reliably index how networks instantiated during specific cognitive function differ across these populations.

Evidence of task-dependent connectivity modulation in SCs agrees with the observation of a decoupling between auditory and occipital regions during a visual task (Eckert et al., 2008). Crossmodal inhibition between auditory and visual cortices has been shown to take place during both auditory and visual stimulation (Laurienti et al., 2002). Clues as to the mechanisms underlying these results come from electrode recordings in mice revealing that auditory stimulation triggers inhibitory GABAergic release in V1 (Iurilli et al., 2012). In case of early blindness, it might be hypothesized that this inhibitory modulation of occipital regions triggered by sound switches to an excitatory state in the absence of competitive visual input during development (Collignon et al., 2009). Potential anatomical structures or physiological processes responsible for EB's increased occipito-temporal connectivity include rewired or reinforced thalamo-cortical pathways as well as direct cortico-cortical connections between primary sensory cortices (Bavelier and Neville, 2002; Collignon et al., 2013; Karlen et al., 2006; Klinge et al., 2010; Shimony et al., 2006; Qin and Yu, 2013). It is worth noting here that sounds also has the potential to increase occipital activity even in sighted individuals in the context of audio-visual stimulation (Giard and Peronnet, 1999; Mercier et al., 2013; Rohe and Noppeney, In press) and that direct connection between primary auditory and visual cortices also exist in the absence of visual deprivation (Falchier et al. 2002, Rockland and Ojima, 2003). The observation of enhanced occipito-temporal connectivity in EBs during an auditory task is congruent with the plethora of task-dependent studies highlighting the functional involvement of EBs' occipital

cortex in auditory processing (Burton, 2003; Collignon et al., 2007; 2009; 2011; Weeks et al. 2000). Similarly, dynamic causal modeling studies show greater cortico-cortical connectivity between these regions in EBs than in SCs when participants are involved in auditory processing (Collignon et al., 2013; Fujii, 2009; Klinge et al., 2010). Finally, a recent magnetoencephalographic study showed that processing auditory inputs in blind produces stronger neural synchronization between auditory and visual cortices in the gamma band, suggesting that the deprived visual cortex is integrated into a larger network related to its new auditory function (Schepers et al., 2012).

At rest, FC between occipital and temporal regions tended to be lower for blind compared to sighted people, a finding that replicates several previous studies (see Bock and Fine, 2014 for review). What could explain EBs' heightened occipito-temporal coupling during task while still shedding light on the reduced RSFC at rest? We hypothesized that one potential solution may reside in the fact that the occipital cortex of EBs involves in multiple independent functional modes. Evidence of cerebral regions involved in multiple overlapping functional modes exists, which notably manifests by the fact these regions switch membership between different temporally independent networks (Duncan and Owen 2000; Smith et al., 2012). This leads to temporally variable connectivity patterns for a specific region (see Hutchison et al., 2013a for a review), a perspective not addressed by using an entire fMRI run to compute of a single FC value per connection. By combining the contribution of all these modes, this single FC value obscures the true underlying functional organization of the brain (Hutchison et al., 2013b; Smith et al., 2012), likely underestimating the effective coupling between functional units. In EBs, the involvement of the occipital cortex in a large number of functional modes is already supported by studies showing its implications in various sensory and cognitive tasks

including auditory and tactile processing as well as language, attention and episodic memory (Amedi et al., 2003, 2004; Bedny et al., 2011; Collignon et al., 2013; Burton, 2003; Gougoux et al., 2009; Noppeney, 2007; Pietrini et al., 2003; Raz et al., 2005). Therefore, lower occipito-temporal RSFC in EBs may result from the implication of their occipital lobe in a greater number of modes, attenuating FC while the brain is free to explore many modes (at rest), and unveiling the importance of these connections while modes are constrained (during a task). Based on the idea that, while at rest, cerebral regions involved in multiple modes would show increased FC variability across time with various networks (Allen et al., 2012), we measured the variability in occipito-temporal FC in both populations for the RS data. In agreement with our hypothesis, an occipito-temporal connection that was modulated by cognitive-states differently in EBs than in SCs also showed a higher variance in functional connectivity across time in EBs than SCs (Fig. 5). Interestingly, our data also supports the presence of this effect across all occipito-temporal connection's since there was a strong and significant correlation between a connection's temporal variability and its modulation effect (Fig. 6). Importantly, it supports the idea that partition in multiple modes (e.g. FC of high temporal variability), might shadow a region's true potential within a network, which in turn can be unveiled during participation to specific tasks.

Another, but more speculative, possibility to explain lower occipito-temporal RSFC in EB, not mutually exclusive with the previous one, is that parts of EBs' occipital cortex form a homogeneous network which is neither modality specific nor task specific. In SCs, studies have revealed the inferior frontal cortex, anterior cingulate cortex and inferior parietal sulci to present such characteristics and lead to the elaboration of the multiple-demand system theory (MD; Duncan and Owen, 2000, see Duncan 2010 for a review). According to this position, these

regions' lack of stimuli, modality, or task specificity makes them an optimal substrate for cognitive flexibility (Fedorenko et al., 2013). Coactivations of the MD system with a variety of task specific networks (Cabeza and Nyberg, 2000) are highly reminiscent of EBs occipital involvement in a collection of sensory and cognitive operations (see for review Frasnelli et al., 2011; Heimler et al., 2015; Ricciardi et al., 2014; Voss et al., 2011). This similarity between the MD system and EBs' extends to how these regions respond to attentional demands. In SCs, fMRI studies show activations of MD regions to stimuli of various modalities when they are attended but not when they are unattended (Hon et al., 2006). Similarly, occipital responses to auditory and tactile stimuli have been shown to be dependent upon the attentional focus in EBs (Kujala et al., 1995; 2005; Sadato et al., 1996; Weaver and Stevens, 2007). However, this is also true of early sensory areas (Kastner et al., 1999). Finally, further support as to the involvement of EBs occipital lobe with the MD system comes from a number of RSFC studies which evidence stronger coupling between frontal areas, which seem congruent with those belonging to the MD system and executive functions, and the visual cortices (Bedny et al., 2010; 2011; Burton et al., 2014; Deen, et al., 2015; Liu et al., 2007; Wang et al., 2013). Still, the true hallmark of the MD system is that its neurons rapidly reorient their response tuning to task relevant features (Duncan, 2010), a fact which has, to our knowledge, never been investigated in EBs. Thus, though the similarities between the MD system and EBs' occipital lobes may be seductive, further research is required to investigate this point.

Our results therefore open new avenues of research on the connectivity of the occipital cortex of the blind and raise attention on the fact that group differences in connectivity measures inferred from resting-state do not readily generalize to specific task-dependent brain-state (e.g. auditory processing). In particular, our study provides a simple foundation for analyses of state-

dependent changes in connectivity in visually deprived individuals. The importance of our results goes beyond the study of blindness by extending a flourishing number of studies (Çetin et al., 2014; Nair et al., 2014) highlighting how inferring the functional connectivity profile of a region solely based on RS data is subject to caution.

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Figure captions

Figure 1. Steps of analyses. A) Preprocessed times series. B) Auditory task activations are modelled out of the task dataset. The modelisation is done at the voxel level independently for each participant and task. The resulting residuals are used as surrogate time series for the following analyses. C) Clustering of voxels using BASC. The clustering algorithm uses time series from both cognitive states and populations. D) Sliding-window analysis carried on RS data from EBs and SCs. Time series within windows of 21 TRs (broken line square) are extracted at the voxel level for each participant. This results in multiple time series per voxel per fMRI run (rest and task). E) Cluster averaged time series. Time series of all voxels within a cluster are. F) Computation of connectivity between the temporal cluster and the occipital ones. Graph axes are labeled with “i” for intensity, “t” for time, and “w” for time windows.

Figure 2. Results from the functional parcellation of the brain into 50 regions shown on a surface (A) and brain slices (B). Regions of interest selected for investigation of occipito-temporal FC, the temporal region and 7 occipital regions (D), are shown on a surface (C) and brain slices (D).

Figure 3. Group average and standard error of FC’s modulation effect [task – rest] for each connection between the temporal region and the 7 occipital regions. * $q < 0.05$ FDR corrected

Figure 4. For the COI analysis, between-group differences in FC’s modulation effect [EBs(task – rest) vs SCs(task – rest)]. A, B) Maps show two regions, 1) middle occipital gyrus, and 2) superior occipital gyrus, for which the connectivity with the auditory regions was differently

modulated by cognitive states in SCs versus EBs. Data is shown both on surfaces and brain slices. C) Plots show FC during rest and during the auditory task for both groups. Only significant interactions are plotted ($q < 0.05$, FDR corrected). Error bars represent standard errors.

Figure 5. Results from the temporal variability (sliding windows) analysis of the resting-state run. Each column represents the variability in FC between the auditory region and one of two occipital regions. These are the same two connection which were differently modulated by cognitive states in EBs when compared to SCs. Error bars represent standard errors.* $p < 0.05$

Figure 6. Correlation between the average difference in modulation across groups [EBs(Task – Rest) – SCs(Task – Rest)] and the average difference of FC variability across groups. Each black data point represents a single occipito-temporal functional connection (Correlation significant at $p < 0.005$). Each gray data point represent the strength of a single functional connection between two regions not found within the occipital mask (Correlation was non-significant, $p = 0.16$).

Figure 1.

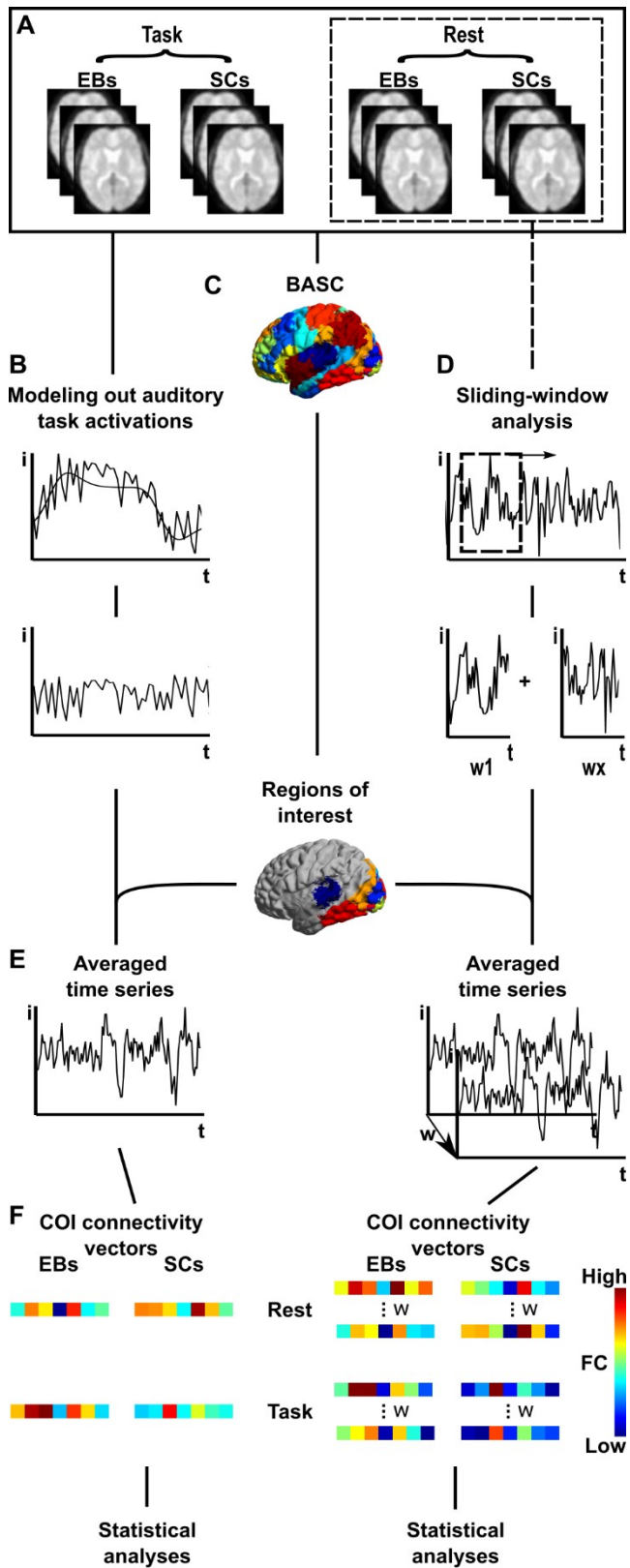


Figure 2.

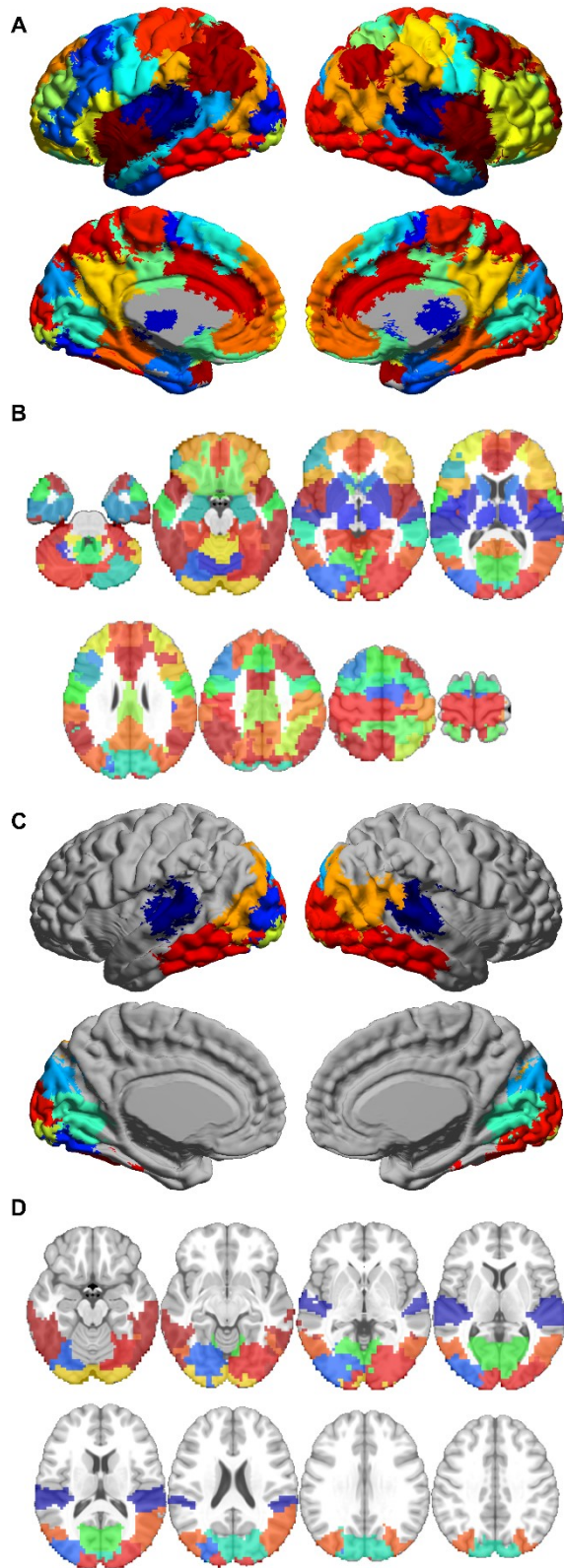


Figure 3.

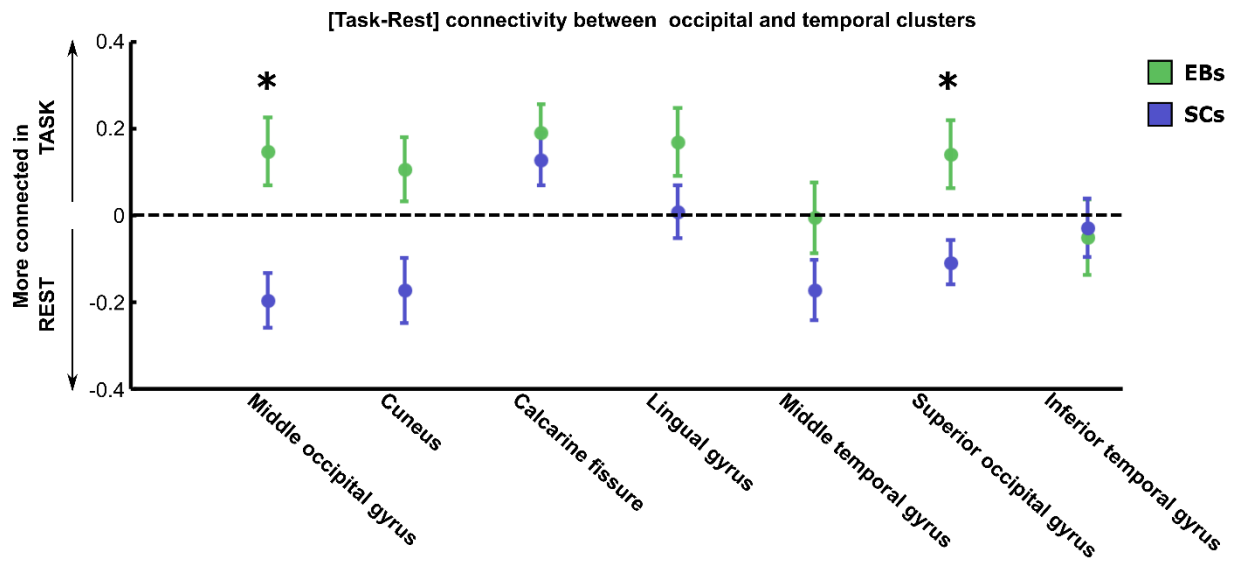
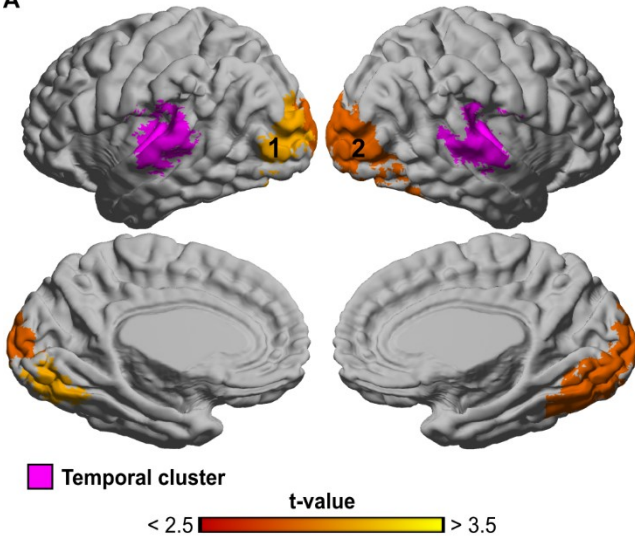
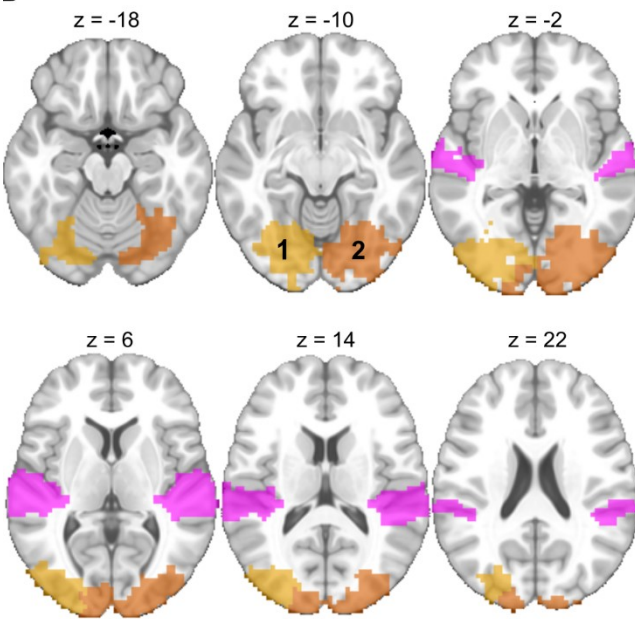


Figure 4.

A



B



C

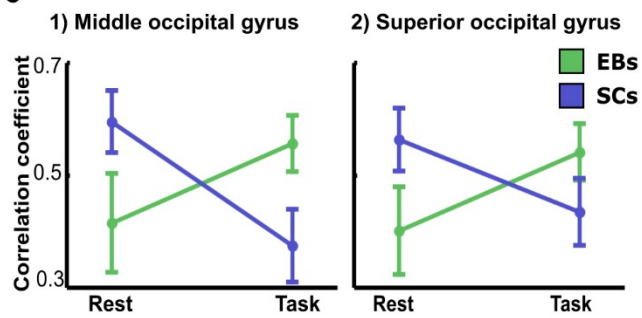


Figure 5.

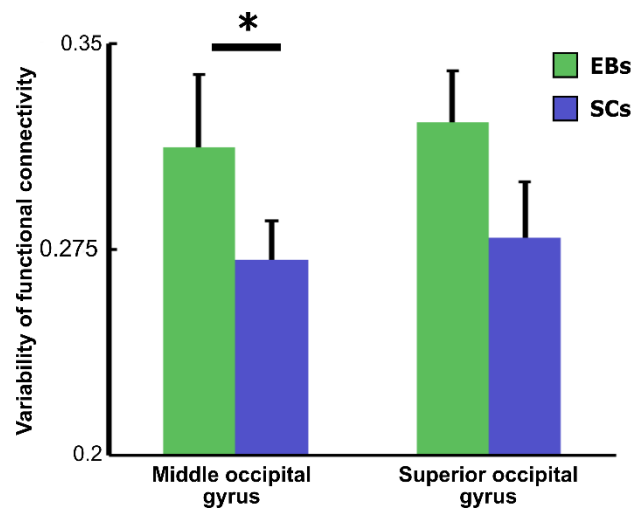
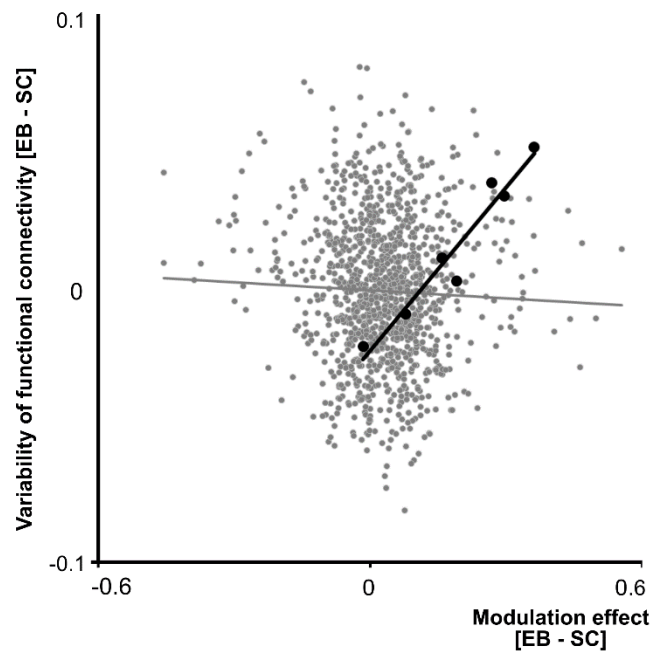


Figure 6.



Supplementary material.

Supplementary tables

Supplementary table 1. Characteristics of the blind participants.

Participant	Age (y)	Sex	Hand	Residual vision	Onset	Cause of blindness	Education	Musical experience
CB1	40	M	R	No	0	Fibroplasia	University	Yes
CB2	61	M	R	Diffuse light	0	Congenital cataracts	University	Yes
CB3	56	M	R	No	2 months	Electric burn of optic nerve	High school	No
CB4	26	M	R	No	0	Leber's congenital amaurosis	University	Yes
CB5	54	M	R	No	0	Glaucoma	University	Yes
CB6	38	M	R	No	0	Detached retina	High school	Yes
CB7	39	M	R	Diffuse light	0	Leber's congenital amaurosis	University	No
CB8	27	F	A	No	0	Retinopathy of prematurity	High school	No
CB9	56	F	R	No	0	Retinopathy of prematurity	High school	Yes
CB10	32	F	R	No	0	Glaucoma	High school	No
CB11	48	M	R	No	0	Thalidomide	University	Yes
CB12	31	F	R	No	3 years	Retinoblastoma	College	No
CB13	43	M	R	No	0	Glaucoma and aniridia	University	Yes
CB14	46	M	R	No	0	Congenital cataracts and glaucoma	University	Yes

Supplementary table 2. Central coordinates and average radius in standard deviation of temporal and occipital networks at resolution 50.

Network number and region's name	Left hemisphere				Right hemisphere			
	x	y	z	Approximate radius(mm,sd)	x	y	z	Approximate radius(mm,sd)
25. Superior temporal gyrus	-52	-23	9	5,00	55	-25	11	4,94
37. Middle occipital gyrus	-28	-81	2	5,80	-	-	-	-
38.Cuneus	-12	-81	30	4,85	16	-82	28	4,56
42. Calcarine fissure	-13	-67	6	4,34	14	-68	6	4,78
43. Lingual gyrus	-25	-86	-16	7,55	30	-80	-20	9,20
46. Middle temporal gyrus	-42	-68	19	8,81	47	-64	16	7,53
47. Superior occipital gyrus	-11	-95	10	3,73	26	-82	-1	7,32
50. Inferior temporal gyrus	-50	-42	-17	7,28	56	-37	-18	9,49

Supplementary table 3. Average and standard deviation of fisher transform of correlation coefficient for each occipito-temporal functional connection investigated.

Functional connectivity between temporal cluster (#25) and:	Early blind participants						Sighted controls					
	Rest		Task ¹		Task ²		Rest		Task ¹		Task ²	
	M	SD	M	SD	M	SD	M	SD	M	SD	M	sd
37. Middle occipital gyrus	0,416	0,080	0,557	0,052	0,564	0,056	0,595	0,048	0,375	0,059	0,400	0,065
38. Cuneus	0,594	0,053	0,700	0,071	0,702	0,077	0,585	0,048	0,393	0,070	0,413	0,076
42. Calcarine fissure	0,535	0,075	0,725	0,052	0,727	0,061	0,546	0,069	0,658	0,054	0,673	0,057
43. Lingual gyrus	0,211	0,065	0,370	0,045	0,377	0,047	0,395	0,061	0,396	0,032	0,405	0,029
46. Middle temporal gyrus	0,638	0,082	0,635	0,081	0,632	0,081	0,704	0,055	0,510	0,067	0,532	0,073
47. Superior occipital gyrus	0,402	0,079	0,542	0,053	0,543	0,056	0,564	0,03	0,435	0,054	0,456	0,060
50. Inferior temporal gyrus	0,444	0,094	0,382	0,084	0,395	0,084	0,450	0,073	0,404	0,049	0,424	0,052

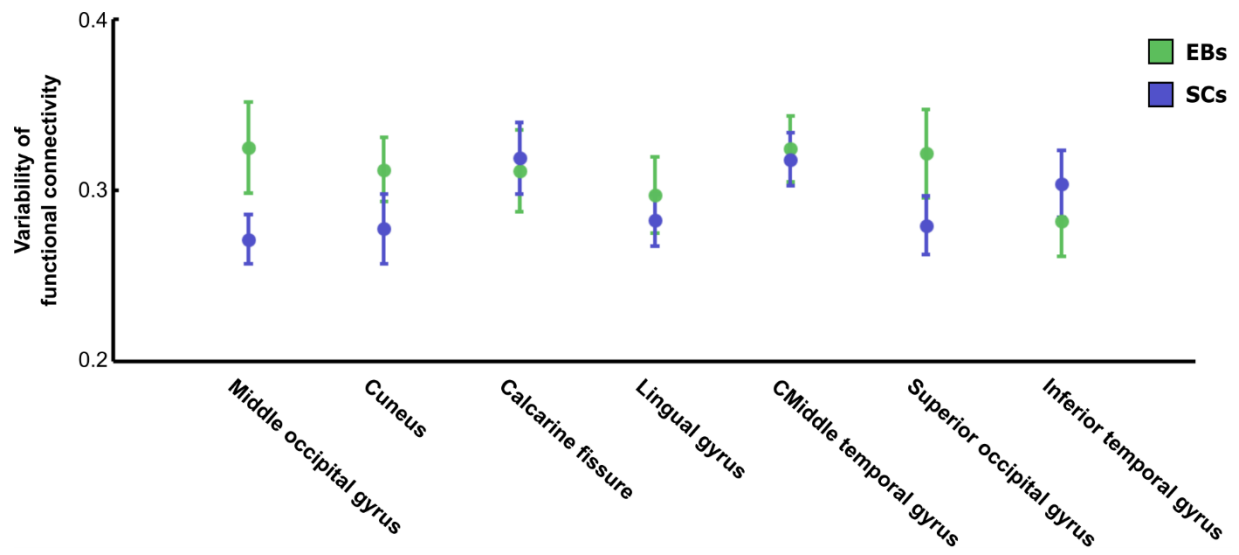
¹ Task run with the effect of block modeled out of the time series.

² Task run with basic preprocessing.

Supplementary figure captions

Supplementary figure 1. Group average and standard error of FC temporal variability at rest for each functional connection between the temporal region and the 7 occipital regions.

Supplementary figure 1.



Article #3

Contribution des auteurs

Maxime Pelland: Rédaction de l'article, collecte des données, analyse des données et conceptualisation de l'étude.

Diana Cárdenas : Rédaction de l'article.

Emma Campbell : Rédaction de l'article.

Franco Lepore: Conceptualisation de l'étude et financement en tant qu'investigateur principal.

Enhanced familiar voice processing irrespective of explicit speaker identification.

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Abstract

Every speaker's voice contains its own idiosyncrasies, making it unique. Notwithstanding, auditory cortices process these speaker-specific variations with incredible ease, allowing to distinguish speech from speaker identity. This is especially true for personally known voices which are more easily understood than those unknown to the listener. However, little is known about the factors required for this *familiarity effect* to take place. In two experiments, we investigated, using single phonemes, whether participants needed to be aware of who they were listening to, and whether they needed to know that they were listening to human voices for the familiarity effect to take place. The task used involved discriminating voices from piano notes in a noisy environment. Results from experiment one showed that, even in noisy conditions which precluded participants from identifying familiar speaker identity, personally known voice were still more easily discriminated from piano notes than the voices of unknown speakers. However, results from experiment two show that when participants were unaware that they were listening to voices, the advantage that familiar voices disappeared. These results support the notion that the cues necessary for listeners to implicitly recognize a speaker are present even in short vocal stimuli such as phonemes. Moreover, they provide important clues as to the neuronal mechanisms implicated in the familiarity effect.

Keywords: voice, familiarity, masking, identification, implicit recognition.

1. Introduction

The human voice is an exceptionally key tool in social interactions, its most evident role being to carry speech. However, this is far from its sole social function. Arguably as importantly, voices contain paralinguistic and extralinguistic cues related to gender, affective states and, critically, speaker identity or familiarity (for comprehensive reviews see Belin, Fecteau & Bédard, 2004 and Schweinberger, Kawahara, Simpson, Skuk, & Zäske, 2014). Although the processing of these cues has historically been taken to be done by independent processes (Joos, 1948), recent findings have shown that a speaker's vocal and/or phonetic idiosyncrasies (SVPI) can significantly influence a listener's speech processing. By highlighting the interdependence between these SVPIs and speech processing, studies open new and interesting avenues of investigation.

Inklings of a relationship between SVPIs and speech come from studies investigating which acoustical features influence speaker discrimination and perceived similarity. For example, using multidimensional scaling, the perceived dissimilarity or between pairs of speakers has been shown numerous time to be related to a speakers' characteristic formant frequencies (Masumoto, Hiki, Sone, & Nimura, 1973; Murry & Singh 1980; Kreiman, Gerratt, Precoda, & Berke, 1992; Baumann & Belin, 2010; Nolan, McDougall, & Hudson, 2011). The same formants are also crucial to speech perception; they consist of spectral features needed to distinguish different vowels which vary slightly from speaker to speaker.

The relationship between speech and SVPIs has also been hinted at by studies directly investigating their contingency. For instance, experiments demonstrate that SVPI representations influence the identification and retention of spoken words (Goldinger, Pisoni, & Logan, 1991; Palmeri, Goldinger, & Pisoni, 1993; Church & Schacter, 1994; Sheffert, 1998).

More strikingly, individuals can reliably identify speakers whom they are personally familiar with even when the voices are resynthesized to contain a limited number of pure tones (3-4) (Remez, Fellowes, & Rubin, 1997; Sheffert, Pisoni, Fellowes, & Remez, 2002). These sinewave sentences feel completely unnatural and lack any voice quality, however their phonetic attributes are relatively spared, leaving them intelligible. Together, these observations demonstrate the perceptual interdependence of SVPIs and speech.

Improved vocal processing resulting from SVPIs is especially remarkable when the speakers are personally known to the listener, or when listeners are trained to recognize a subset of voices. For example, multiple studies have shown better speech recognition (Nygaard, Sommers & Pisoni, 1994; Nygaard & Pisoni, 1998; Yonan & Sommers, 2000; Pilotti, Beyer, & Yasunami, 2001; Souza, Gehani, Wright, & McCloy, 2013), and attentional capture (Barker & Newman, 2004; Newman & Evers, 2007) for speakers whose SVPIs are familiar to the participants than for novel speakers. This relationship between speaker familiarity and improved voice processing is especially relevant to model how the human brain analyzes voices. However, without knowing the factors needed for this *familiarity effect* to take place, its underlying mechanisms remain hidden.

It has been suggested that such a factor might be the listener's ability to explicitly identify the speaker during a concurrent vocal task (e.g.: speech shadowing, see Newman & Evers, 2007). In contrast, other results suggest that word identification is improved even when listeners cannot explicitly identify familiar speakers (Yonan & Sommers; Newman & Evers, 2007; Souza et al., 2013). However, these studies were unable to fully conceal the speakers' identity from participants: an important number of participants successfully identified the speakers in each study, thus weakening their conclusions. Only Souza and colleagues (2013)

showed that participants who did not explicitly identify the familiar speakers still presented evidences of a familiarity effect. Yet, no statistics were reported for this particular subset of subjects.

A second factor that might influence the familiarity effect is its reliance on top-down mechanisms. Specifically, the effect might be contingent upon a listener's awareness to the fact that they are hearing human voices. Indeed, it has been shown that expecting to observe stimuli from a specific category is linked to improved perceptual discrimination (Esterman & Yantis, 2010) which probably arises from top-down modulation of sensory cortices. If participants are not expecting to hear human voice, then the top-down mechanisms implicated in the familiarity effect might not be engaged.

Thirdly, the exact SVPIs responsible for the familiarity effect are still unknown. Results from Nygaard & Pisoni (1998), suggest that they might arise from cues found solely within sentences and single words. However, it is still unclear whether they are solely dependent on prosodic, socio-linguistic, idiolectic, or phonemic and allophonic segmental idiosyncrasies found in long utterances or if they arise from other types of SVPIs present in short vocal sound such as single phonemes.

Thus, the main goal of the present study is to investigate the limits of the familiarity effect to better understand its underlying mechanisms. Specifically, we evaluated whether the effect is dependent upon the explicit recognition of a voice, upon a listener's awareness that voices are being heard, and upon SVPIs found in single phonemes. To assess the impact of these three factors on the familiarity effect, two experiments were carried using a discrimination task we developed. The task consisted of discriminating between the phoneme /a/ and piano notes. To preclude speaker identification, but allow voice discrimination, a broadband noise was added

to the background to mask the stimuli. In both experiments, familiar voices consisted of voices from people whom the participants had known from a minimum of 3 years (familiar voices). In the first experiment, participants underwent the discrimination task, aware that they would be hearing voices but unaware that one was going to be from familiar speaker. During debriefing, participants were asked whether they had noticed the presence of a familiar voice amongst the stimuli. A subset of participants underwent a speaker identification task to establish whether they could implicitly recognize the familiar voice. During the second experiment, participants completed the discrimination task without being told that they would be hearing voices.

If the familiarity effect extends to single phonemes, and is present even under implicit voice recognition, we would expect familiar voices to be discriminated more easily from piano notes than unfamiliar ones even under conditions precluding all participants from explicitly identifying the familiar voices (Experiment 1). Finally, if the mechanisms underlying the familiarity effect are not contingent upon top-down effects, we hypothesize that familiar voices should be more easily discriminated from piano notes even when participants are unaware that they are hearing voices (experiment 2).

2. Experiment 1

The goal of experiment 1 was to investigate whether the familiarity effect would be present when participants do not explicitly recognize the familiar speaker. To do so, participants were asked to complete two tasks. In the first, they had to discriminate familiar and unknown voices from piano notes. If the processing of familiar voices is influenced by the familiarity effect, they should be easier to discriminate from piano notes than unknown voices. Participants were then debriefed and asked whether they had recognized a voice as being familiar. To further

investigate whether it was truly impossible to explicitly identify the familiar voice during the first task, participants underwent a second task in which they heard multiple voice and had to identify which one was familiar.

2.1 Methods

2.1.1 *Participants*

Sixteen individuals (8 females) aged between 18 and 30 participated to this experiment. No participant reported having any hearing problem.

2.1.2 *Stimuli*

Vocal stimuli were recorded from people both familiar and unknown to the participants. Individuals were considered familiar to the participants if they had known them for at least three years and met on average once or more a week. These familiar were referenced by the participants. Voices were recorded in an acoustically shielded room using a condenser microphone (AT2010, Audio-technica), amplified by an analog preamplifier (Audio Kontroal 1, Native Instruments) and digitized at 44,100 Hz by Adobe Audition 1.5 (Adobe Systems Inc.). People being recorded were asked to repeatedly pronounce the phoneme /a/ during 1 s. An average number of 10 repetitions were recorded per participants. Participants were asked to repeat the exercise if they pronounced the wrong phoneme or if they seemed to alter their voice during the recording. An experimenter listened to each vocal sample, compared it to a natural sample of the speaker's speech, and selected the one most typical of the speaker's voice.

The selected voice samples were cut to a length of 212 ms with a 5 ms silence at the beginning. Otherwise, the attack of the sound was kept intact. The fall of the stimuli was

attenuated using a spline function. Stimuli were low-pass filtered at 10,000 Hz using a fast Fourier transform.

Subsequently, the selected recordings were paired with synthesised piano notes based on their fundamental frequency (F0). These 1 s long stimuli were obtained using Sibelius 5 (Avid Technology, Inc.). The first 212 ms were kept, low-pass filtered at 10 kHz. Moreover, two more steps were taken to reduce the perceived differences between piano and vocal stimuli. First, for the piano notes, frequencies between 2 and 3 kHz were attenuated to 80% of their intensity because it was observed that most piano stimuli showed higher intensity at these frequencies when compared to voices. Second, the temporal envelop of the voices was applied to their paired piano notes to prevent participants from differentiating the two stimuli based on their temporal shape.

Voices unknown to the participants were chosen from a pool of 60 tokens recorded for this experiment. For each participant, three voices were selected. Each had to be paired to a different piano key, yet possess a fundamental frequency and first formant frequency (measured by Praat, Boersman & Weenink, 2013) as similar as possible to those of the familiar voice. The fundamental frequency and first formant frequency were chosen to minimize the perceived differences between the vocal samples (Baumann & Belin, 2010). Thus, for each participants, four voices were used: three unknown and one from a familiar speaker whom they had referred to the experimenters.

All stimuli were normalized for the root mean square (RMS) using a 125 ms window and the equal loudness contour option provided by Adobe Audition 1.5. This option uses dB A weights to equalize RMS, a method which gives different weights to different frequencies as a function of how sensible humans are to each.

2.1.3 Procedure

2.1.3.1 Task 1, voice/piano key discrimination

Participants were comfortably seated in an acoustically shielded room with their head placed on a chin rest. They responded to a two alternatives forced choice in which two stimuli, one voice and one piano key, were presented; participants had to identify whether the voice stimuli was presented before or after the piano key. Participants were told that the familiar voice that had been recorded would not be present in this task but would be used in the subsequent one. However, unknown to them, the familiar voice, the three unknown voices, as well as their matching piano notes, were presented with equal probabilities.

A broadband masking noise (BN; ~50 – 10,000 Hz) was presented during the whole experiment. It was continuously and concurrently produced by 4 commercial loudspeakers placed at 45°, 135°, 225° and 315° on the azimuth of the participants and placed at the same height as the participants' head (see Figure 1 for experimental setup). Each loudspeaker was set to produce the BN at 55 dB SPL. The total noise level was ~60 dB SPL. Speakers produced independent BN (uncorrelated) giving the impression that the noise had no single point of origin. The experimental setup is illustrated in Figure 1.

Insert figure 1 approximately here

Each trial consisted of a voice and a piano key separated by an inter-stimuli interval of 1.5 s. The order of the pair was randomly assigned. No time limit was set for trials in order to avoid time constraint from affecting accuracy. Subsequent trials started 0.5 s after an answer button was pressed by the participant on the previous trial. Stimuli were produced by a

commercial loudspeaker placed directly in front of the participants at the same height as their head and at a distance of 60 cm. Stimuli pairs were randomly presented at various signal-to-noise ratios (SNR) so that a psychometric curve could be fitted to their data during data analysis. The SNRs were -31.5, -28, -24.5, -21, -17.5 and -14 dB for the first six participants. However, using these parameters, the lowest and highest SNRs were barely distant enough to capture the psychometric curve adequately. Thus, it was decided to use a seventh SNR (-34.5). Moreover, when a participant correctly answered to less than 66% or and more than 84% within the first 100 trials, the difficulty of the task was modified by increasing or decreasing each SNRs by a few dB (1 to 3). Doing so, we ascertained that the SNRs were roughly centered on the SNR at which a participant was able to discriminate piano notes from voices 75% of the time. Such a choice has been shown to improve the estimate of psychometric curves (Wichmann & Hill, 2001a). A total of 80 trials were presented at each SNR. Thus, there were 20 trials for each voice at every SNRs.

The stimuli were presented in four blocks of approximately six minutes each. Short 1-2 minutes pauses were taken between each block. After the task was completed, participants were asked whether they had realised that one of the voices was familiar. None of them did.

2.1.3.2 Task 2, speaker identification

To investigate whether participants were able to recognize the familiar voice even though they did not report being able to, a subset of six participants underwent a 3 alternatives forced choice task. Though small in number, the subset of this magnitude was deemed acceptable since the inter subject variability was low enough for high statistical significance to be reached (see results), and the task only sought to support the finding that none of the

participants reported having noticed the presence of a familiar voice (see above). During this task, participants heard three vocal stimuli taken from the previous task which always included the familiar voice. Stimuli were presented in a random order. Once all three voices were presented, participants had to indicate which of the three the familiar voice was. A 1.5 s inter-stimuli interval separated each stimulus from the subsequent one in the trio. A 1 kHz tone was presented 0.5 s before the onset of the trials.

The speaker identification task was separated in three conditions. Each condition consisted of a single block containing 30 trials (see table 1 for a summary of each condition). A different SNR was used in each condition and was tailored to the participants' scores on the previous task. That is, the intensity of the vocal stimuli was set to specific SNRs dependent upon the SNR at which each participant obtained a score of 90% correct answers (SNR90%). This specific threshold was selected so as to make sure that all stimuli would be presented at an SNR which allows participants to reliably perceive voices. In order to evaluate SNR90%, a normal cumulative distribution function was fitted to the data from the piano/voice discrimination task (see analysis section).

Insert table 1 approximately here

Then, during the speaker identification task, stimuli were presented 5 dB SPL over SNR90% in the first block and third block, and 13 dB SPL over SNR90% in the second block. Similarly to the discrimination task, stimuli in blocks 1 and 2 were masked by a BN produced by four loudspeakers surrounding the participants. No masking noise was used in the last block in order to ascertain that participants could identify the familiar voice in silence.

2.1.4 Analyses

2.1.4.1 Task 1, voice/piano key discrimination

For each participant and SNR at which stimuli were presented, the percentage of correct answers for the unknown voices was computed as the average number of correct answers for trials in which unknown voices were present. The resulting data were then fitted with a normal cumulative distribution function.

For every participant, the best fit curve was used to estimate the SNR at which the percentage of correct answers was 75% (SNR75%). For the statistical tests of the discrimination task, SNR75% was used instead of SNR90% because it better describes the data (Wichmann & Hill, 2001b). The same analyses were carried for results from trials containing the familiar voice.

Analyses were carried a second time to estimate SNR90%, the point at which a participant could correctly discriminate piano notes from voices with an accuracy of 90%. This threshold was used for the speaker identification task (see above).

2.1.4.2 Task 2, speaker identification

Results from the speaker identification task were simply carried by computing the percent of correct response for each condition separately.

2.2 Results

2.2.1 Voice/piano key discrimination task

For the voice/piano key discrimination task, a paired sample t-test was used in order to investigate the difference in SNR75% between familiar voices and unknown voices. Results show that the SNR75% was significantly lower (better) for familiar voices (mean -26.77, s.d.

4.74) [$t(15) = 2.841, p = .012, d = 0,71$] than for unknown voices (mean -25.41, s.d. 4.60; see Figure 2). Thus, familiar voices were more easily discriminated from piano notes than unknown voices. These results reflect the presence of the familiarity effect which arises from improved auditory processing following familiar voice recognition (whether implicit or explicit).

Insert figure 2 approximately here

2.2.2 Speaker identification task

For the speaker identification task, a one way repeated measure ANOVA was used to investigate differences in the identification rates of each condition. The results showed a significant effect of condition [$F(2,10) = 600.2, p < .001$]. That is, the lower the SNR, the harder it was to identify the familiar voice. Using an LSD correction for multiple tests, post-hocs were carried out to investigate whether all conditions differed in their difficulty. The silence condition showed a higher percentage of correct answers (mean 0.955, s.d. 0.065) than the 13 dB SPL over threshold condition (mean 0.250, s.d. 0.072) [$t(5) = 23.26, p < .001$] and the 5 dB SPL over threshold condition (mean 0.106, s.d. 0.057) [$t(5) = 27.66, p < .001$]. There was also a significant difference between the two noise conditions [$t(5) = 10.27, p < .001$]. Thus, none of the conditions were equally challenging. This result is to be expected since each were carried at different SNRs, making them more or less challenging.

Student's t-tests were used to investigate whether participants were able to identify voices during the task. Specifically, if they answered randomly, their score should be around 33% correct responses, whereas if they were able to identify the voice correctly, their scores

should be above 33%. Results showed that all three conditions did differ from the 33% mark; the 5 dB SPL over threshold condition average was lower than 33% [$t(5) = -9.58, p < .001$]. Similar results were found for the 13 dB SPL over threshold condition [$t(5) = -2.71, p < .05$]. Lastly, the percentage of correct answers in the silence condition was highly above chance [$t(5) = 23.38, p < .001$]. Results from the speaker identification task are summarized in Figure 3. Briefly, in the presence of masking noise, participants were biased toward classifying the familiar voices as being unknown. Thus, they were unable to explicitly recognize them. Since the voice/piano key discrimination task was carried in higher SNRs than condition 1 and 2 of the current task, the results support the idea that the voice/piano discrimination task was carried under conditions which precluded the identification of familiar voices. Moreover, the finding that familiar voices were easily identified in the silent condition shows that the stimuli's quality was sufficient for them to be identified.

Insert figure 3 approximately here

3. Experiment 2

Experiment 2 was designed to further test the requirements needed for the familiarity effect to be mobilized. Specifically, the experiment aimed at testing whether participants could better discriminate piano notes from familiar voice than unfamiliar ones even when unaware that they were hearing voices. Therefore, it investigates whether specific top-down modulations of auditory cortices must be in place for the effect to be mobilized. The same voice/piano

discrimination task as in experiment 1 was used. However, participants were not told that half of the stimuli they would hear consists of voices, only that there would be piano notes and an unnamed sound. If the improved processing underlying the familiarity effect takes place even in such a situation, we would expect the familiar voices to be less often mistaken to be piano notes, and thus to be more easily discriminated from them.

3.1 Methods

3.1.1 Participants

Sixteen individuals (12 females) participated in this study. They were all aged between 18 and 30. None reported having any hearing trouble.

3.1.2 Stimuli

Stimuli were acquired as in experiment 1, and were processed in the same way. Briefly, a familiar voice was recorded for each participant and paired to a piano key of similar fundamental frequency. Three other voices, unknown to the participant and each paired to a different piano key, were also selected. Thus, in total, each participant heard a total of 4 different voices and piano notes during the experiment. Each stimulus was 212 ms long and low-pass filtered at 10 000 Hz. The amplitude of piano notes for frequencies between 2 and 3 kHz were also attenuated. The rise of the voice was kept intact, but its fall was faded. The temporal envelop of a vocal token was applied to its paired piano key.

3.1.3 Procedure

Participants solely underwent the piano key/voice discrimination task. The procedure differed from experiment 1 only by the instructions that were given to the participants. They were told that they would be hearing pairs of sounds which contained an unknown sound as well as a piano key. To alleviate any suspicions as to why the experimenter had recorded the voice of someone known to the participant, they were further told that they would be participating in a second (fictional) task in which they would be identifying the speakers. Participants were informed that the piano notes were slightly modified and they were allowed to listen to a sample of them. Afterward, they identified whether the piano key was presented before or after the other sound. The unknown sounds were voices, including a familiar voice, as in experiment 1. Again, the experiment was separated into 4 blocks.

Stimuli were presented at seven different SNRs which were selected using the same procedure as in experiment 1. Briefly, if participants scored lower than 66% correct answer or higher than 84% during the first 100 trials, the SNRs were adjusted to make the task more or less challenging. A short debriefing at the end of the experiment ensured that no participants had identified the second stimuli as being a voice. Only one participant said that it had come to her mind that the unnamed stimuli might be voices.

3.1.4 Analyses

The same analyses as in experiment 1 were carried. Briefly, a cumulative distribution function was fitted separately for the data from trials containing familiar voices and for the data of unknown voice trials. The resulting best-fit curves were used to estimate the SNR at which a

participant would have discriminated piano notes from voices 75% of the time. This threshold was used for the following statistical comparison.

3.2 Results

As in the first experiment, a paired sample t-test was used in order to investigate the difference between the threshold (percentage of correct answers = 75%) for trials with familiar voices and those with unknown voices. Results show that the threshold was not significantly lower for familiar voices (mean -22.47, s.d. 3.54) [$t(15) = 1.28$, $p = ns$, $d = 0.31$] than for unknown voices (mean -21.65, s.d. 3.54; see Figure 4). This indicates that piano notes presented in pair with familiar voices were not easier to discriminate than piano notes presented in pair with unfamiliar voices. Thus, no familiarity effect was observed. That is, familiar voices were not the target of improved processing when participants were unaware that they were hearing voices. If they had been, they should have been less likely to be mistaken as piano notes, and therefore, trials including familiar voices would have had a lower discrimination threshold than trials containing unknown voices. This experiment, however, did not find evidence that such an effect had taken place.

Insert figure 4 approximately here

4. Discussion

To deepen our knowledge of how a speaker's vocal and phonetic idiosyncrasies (SVPI) affect voice processing, we tested the limits of the familiarity effect. Specifically, we

investigated whether the SVPI responsible for its mobilization are found in single phonemes, and whether the familiarity effect is contingent on implicit speaker identification and on one's awareness to what they are hearing (voices). To do so, participants completed a task consisting of discriminating piano notes from human voice samples in the presence of broadband noise. Presentation of the stimuli at various SNRs allowed us to fit the data with a cumulative distribution function, and to find a subject's voice discrimination threshold for both familiar and unfamiliar voices. In the first experiment, participants were aware they would be discriminating voices from piano notes, but did not know that some of the voices were from personally known speakers. In experiment 2, participants knew they would be hearing piano notes but were unaware that half of the stimuli consisted of voices. In line with our expectations, we observed lower (better) voice discrimination thresholds for familiar than for unknown voices (Figure 2). Notably, we showed for the first time that this effect was present even when participants could not explicitly recognize the familiar voice (figure 3), and that it relies on SVPIs found in phonemes. Moreover, results show that the familiarity effect is absent when participants are unaware of the presence of voices in the experiment (Figure 4).

The lower discrimination threshold for familiar voices than for unknown ones seen in experiment 1, is in agreement with studies showing improved stream segregation and speech processing for sentences and words spoken by familiar individuals (Nygaard et al., 1995; Nygaard & Pisoni, 1998; Yonan & Sommers, 2000; Pilotti, et al., 2001; Newman & Evers, 2007; Souza et al., 2013). This result probably arises from improved processing of familiar voices which made their representations clearer, easing their discrimination from piano notes. Similar results were expected for participants who were unaware of hearing voices (experiment 2), since better representations of familiar voices should have made them less likely to be confused with

piano notes. However, this was not so, the implications of the latter finding are further discussed in the next section.

The most intriguing results of the current study were related to the speaker identification task of experiment 1. Indeed, although participants did identify the familiar speaker in silence on almost all trials, they showed a significant bias toward classifying the same speaker as unknown in the presence of noise (SNR's mean = -17.7) (Figure 3). This unprecedented result is surprising especially when considering that implicit recognition of the familiar voice had to have occurred during the speaker identification task. Indeed, the speaker identification task was carried in much easier conditions than the voice/piano discrimination task (SNRs of -14 to -37) which evidenced the familiarity effect, a marker of implicit voice recognition. To our knowledge, no study concerned with voice processing has ever shown such results. However, recent models of face processing could provide some clues as to what mechanisms might underlie this auditory bias. Indeed, models of voice and face processing possess a large number of similarities (Campanella & Belin, 2007). In their model, Ellis and Lewis (2001) suggest that delusions pertaining to facial identity might arise when two routes of implicit facial recognition provide conflicting information. In vision, these two implicit pathways include one leading to a sense of familiarity with the face, and one creating the appropriate affective response. Thus, it might be that our stimuli were strong enough to activate one route, but not the other, leading to the observed bias. Further investigation will be necessary to evaluate the exact nature of this effect.

4.1 Vocal features inducing the familiarity effect

Our results show for the first time that the familiarity effect is not limited to sentences or words, but that it extends to single vowels. Given that single vowels do not contain sufficient

information for a listener to extract prosodic, socio-linguistic (Ladefoged & Broadbent, 1957), idiolectic, or phonemic and allophonic segmental idiosyncrasies, the familiarity effect must arise from other speaker specific cues. Although no study has investigated which cues these might be, a parsimonious solution would involve SVPIs used to explicitly identify or differentiate speakers. These include, among others, fundamental and formant frequencies (Masumoto et al, 1973; Murry & Singh 1980; Kreiman et al., 1992; Baumann & Belin, 2010; Nolan et al., 2011).

Still, these cues should not be taken as the sole ones responsible for the familiarity effect. Some are found only in longer utterances as Nygaard and Pisoni (1998) have demonstrated by training participants to recognize speakers from sentences and showing that the resulting familiarity effect was present for sentences but did not extend to single words. Thus, the familiarity effect can be engendered by a variety of cues. Further experimentation is required to resolve whether these different cues improve the processing of familiar voices using similar or distinct mechanisms.

4.2 Possible neuronal mechanism underlying the familiarity effect

Our results are the first to show that mobilization of the resources underlying the familiarity effect does not rely on explicit speaker identification or discrimination. This finding suggests a dissociation between neuronal mechanisms involved with speaker identification and those involved in fine-tuning auditory analyses to a specific voice (leading to improved processing of that voice). This hypothesis is supported by studies showing that the memories of SVPIs are stored in different cerebral areas than memories of speaker identity. Specifically, it has been reliably shown that a specific area of the superior temporal sulci specializes in analyzing voices (Belin et al., 2000; von Kriegstein et al., 2004). However, this region, the

temporal voice area (TVA), does not process speaker identity, but acoustical properties of voices. Identity processing is instead carried by the temporal poles and frontal lobe cortices (Andics et al., 2010; Latinus, Crabbe, & Belin, 2011). Thus, the TVA makes for an attractive neuronal substrate for SVPIs storage. Together with our results, these findings provide a tentative role for the nodes responsible for learning the acoustical properties of voices: improving vocal processing of familiar voices, and, incidentally, giving rise to the familiarity effect.

A second possibility is that our task activated speaker identification nodes just enough to initiate the familiarity effect, but not enough for speaker identification to occur (see Bruce & Young and Hanley 2014 for similar view on incremental activation). However, this seems unlikely since activation of speaker identification nodes have generally been taken to follow or co-occur with feelings of familiarity (see Hanley 2014). If such feelings were present, we would have expected them to bias participants toward recognizing the familiar voice during the speaker identification task of experiment 1. However, this was not observed in this experiment.

Our results also suggest that the familiarity effect relies on the awareness that voices are being heard. Even though it is impossible to statistically prove the absence of an effect, the difference in effect sizes between experiment 1 and 2 supports our interpretation. Thus, top-down processes are most likely required for the familiarity effect to surface or, at least, be augmented. It might be that the recruitment of neuronal populations involved in recognizing familiar SVPIs are aided by category-specific neuronal anticipatory-activity. This type of activity has been observed when participants expect to see a certain stimuli category and it leads to improved perceptual discrimination (Esterman & Yantis, 2010). Interestingly, this effect has been observed within the TVA (Bonte et al., 2014), a region likely to store SVPIs mnemonic

traces (see above). Therefore, the current results provide clues as to various mechanisms which might underlie the familiarity effect.

4.3 Conclusion

Overall, improved processing of personally known voices takes place even under conditions which preclude identification of said voices. Moreover, the use of single vowels in this experiments suggests that a variety of cues are responsible for this effect. However, this effect is non-existent when participants are unaware of the presence of voices. These results provide important clues as to the neuronal mechanisms underlying the familiarity effect.

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Table 1. Conditions of the speaker identification task

	Conditions		
	Block 1	Block 2	Block 3
Stimulus amplitude over SNR90%	+5 dB SPL	+13 dB SPL	+5 dB SPL
Presence of masking noise	Yes	Yes	No

Figure captions

Figure 1. Experimental setup. The loudspeaker producing the signal is labelled *stimulus*. Loudspeakers producing the masking noise are labelled BN.

Figure 2. Results from the voice/piano key discrimination task. A) Normal cumulative distributions fitted to results from trials containing either a familiar voice or unknown one. Curves represent the average percentages of correct answers across participants. B) Average threshold (percentage of correct answers = 75%; SNR75%) for trials containing either a familiar or an unknown voice.

Figure 3. Results of the speaker identification task. Dashed line indicates the percentage of correct answers expected from random answers. Symbols indicate significance of differences or results when compared to chance levels, (***) indicates $p < 0.005$, (*) indicates $p < 0.05$.

Figure 4. Results from the voice/piano key discrimination task when participants were unaware that voices were being presented. A) Normal cumulative distributions fitted to results from trials containing either a familiar voice or unknown one. The curves represent the average percentages of correct answers across participants. B) Average threshold (percentage of correct answers = 75%; SNR75%) for trials containing either a familiar or an unknown voice.

Figure 1.

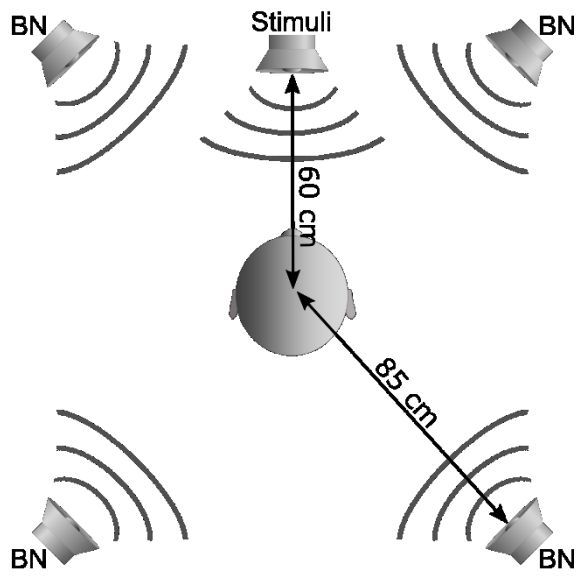


Figure 2.

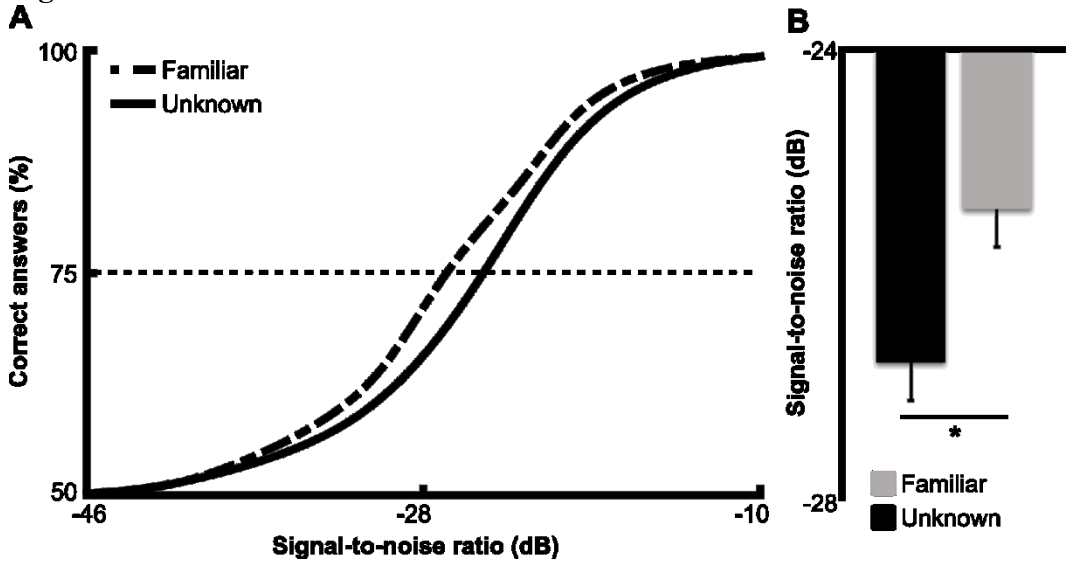


Figure 3

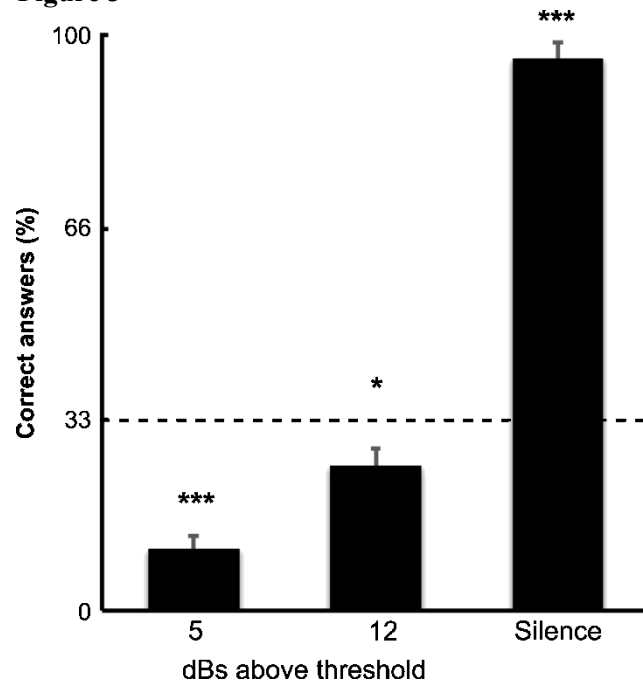
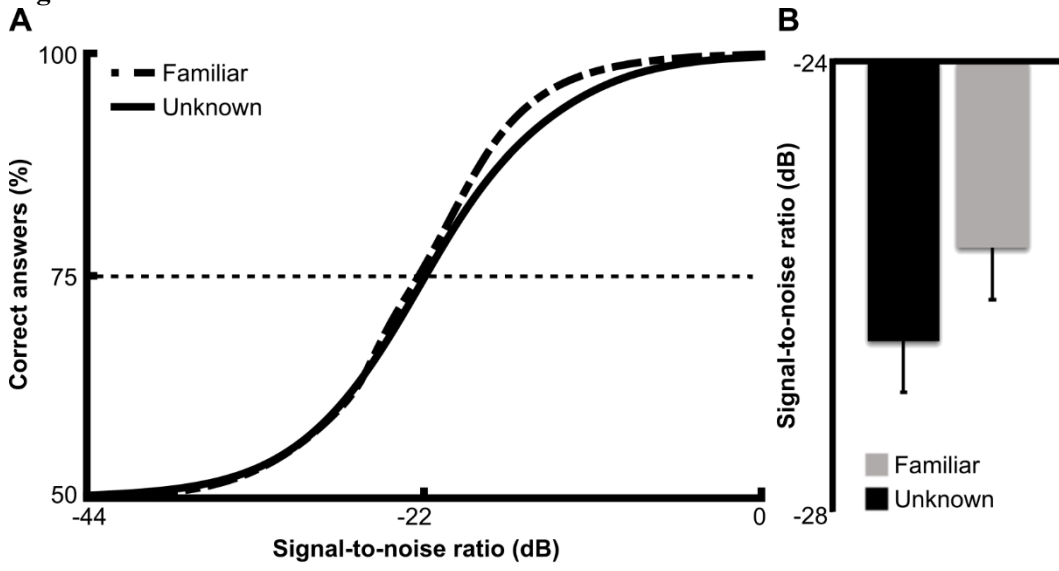


Figure 4.



Discussion générale

Discussion des résultats obtenus

La présente thèse a pour but d'examiner l'impact des entrées sensorielles sur l'organisation des modules fonctionnels (la localisation fonctionnelle) et sur la connectivité fonctionnelle qui lie ces modules (intégration fonctionnelle). Ainsi, les trois expériences qui composent cette thèse ont été élaborées afin d'étudier ces aspects de l'organisation cérébrale chez des personnes atteintes de cécité précoce. Le premier article illustre l'étendue de la réorganisation cérébrale des pôles occipitaux en démontrant l'existence de modules fonctionnels réorganisés au sein de ces régions chez les PNV. Le deuxième article montre que, chez les PNV, les pôles occipitaux présentent des profils de connectivité fonctionnelle différents de ceux des PV. Le troisième article de cette thèse fait suite aux résultats des deux premiers en validant une méthode permettant d'approfondir l'examen des fonctions des pôles occipitaux à l'aide de stimuli vocaux. De surcroît, il démontre l'implication de processus implicites lors de la reconnaissance de voix, une avenue de recherche encore inexplorée chez les PNV.

Premier article

La première étude de cette thèse a comparé la topographie des modules fonctionnels des PNV à celle des PV. Spécifiquement, elle visait à vérifier de manière holistique l'influence de la cécité sur l'établissement et la disposition spatiale de régions cérébrales possédant des fonctions homogènes. Pour ce faire, l'indice de Sørensen et Dice a été appliqué à des partitions extraites de données acquises à l'état de repos. La méthode, développée pour cet article, s'est révélée fiable, présentant des résultats concordant avec la littérature récente et dévoilant des différences entre les PNV et les PV encore inconnues. Brièvement et en accord avec nos hypothèses, les données démontrent que l'établissement de modules fonctionnels ne dépend que

partiellement de la présence d'entrées visuelles; la dépendance étant plus forte pour les régions « visuelles » de bas niveau (cortex visuels primaires et secondaires) que pour les régions « visuelles » de haut niveau (cortex visuels associatifs).

De manière plus spécifique, les partitions représentatives de modules circonscrits et faisant partie des cortex visuels de haut niveau possédaient la même disposition chez les PV et les PNV. Ces résultats supportent l'hypothèse selon laquelle les modules « visuels » de haut niveau se développent intrinsèquement afin de supporter un type d'analyse précis plutôt qu'une modalité (Heimler, Striem-Amit & Amedi, 2015; Ricciardi et al., 2014).

À l'opposé, les régions « visuelles » de bas niveau étaient divisées différemment chez les PNV que chez les PV. Les résultats suggèrent l'apparition d'un nouveau module fonctionnel au sein du pôle occipital droit et l'élargissement du module lié au pôle occipital gauche. Ces résultats sont les premiers à révéler la disposition de ces modules fonctionnels chez les PNV et indiquent que leur développement est influencé par la présence d'entrées visuelles.

La seconde étude de cette thèse vient clarifier le rôle des pôles occipitaux des PNV, car elle révèle que l'intégration fonctionnelle de ces régions est modifiée chez ces derniers.

Deuxième article

Le but principal de la seconde expérience de cette thèse était d'investiguer les résultats contradictoires rapportés par les études de CF et d'activations fonctionnelles chez les PNV. En effet, plusieurs études ont démontré que le lobe occipital est moins fortement connecté aux régions temporelles auditives, et ce, même si tous deux sont activés lors de la perception auditive. Cette incompatibilité apparente a déjà influencé des théories sur la plasticité cérébrale (Burton et al., 2013; Qin et al., 2013), marquant sa source comme vitale à la compréhension des fonctions

des lobes occipitaux chez les PNV. L'un des facteurs pouvant influencer la CF et, donc, potentiellement causer la contradiction entre les études de CF et d'activation, est l'état cognitif des participants.

Ainsi, notre hypothèse était que la communication entre les lobes occipitaux et le cortex auditif temporal serait, chez les PNV, augmentée lors d'une tâche perceptuelle auditive. Nos résultats supportent cette hypothèse en démontrant que l'état cognitif des participants influençait différemment la connectivité occipito-temporale chez les PNV que chez les PV; la connectivité occipito-temporale était plus élevée lors de la tâche qu'à l'ER chez les PNV et plus basse chez les PV. De plus, l'observation d'une forte CF occipito-temporale lors de la tâche auditive chez les PNV supporte leur implication dans des processus perceptuels et démontre que les données d'ER chez les PNV doivent être interprétées avec précaution. Par exemple, l'idée que les lobes occipitaux sont impliqués dans des processus attentionnels plutôt que perceptuels (Burton et al., 2013) n'est plus aussi tenable.

Le second but de cette étude était d'examiner une cause possible de la discordance de CF entre l'ER et la tâche auditive. L'hypothèse était que les lobes occipitaux des PNV participent à un plus grand nombre de réseaux/modes temporaux que celui des PV à l'ER, que cette participation est temporellement variable, passant d'un mode à un autre, et que cette variabilité dans le temps vient noyer la CF réelle liée à chacun des modes. À l'opposé, lors d'une tâche, la CF est représentative de l'intégration fonctionnelle entre deux régions, car les modes temporaux sont restreints à ceux nécessaires à la tâche. Si l'hypothèse est fondée, la CF occipito-temporale à l'ER devrait être plus temporellement variable chez les PNV que les PV. Pour vérifier l'hypothèse, la CF entre différentes régions occipitales et temporales a été mesurée à l'intérieur d'une série de fenêtres temporelles. Ensuite, la variabilité de cette CF a été sujette à des

comparaisons inter-groupes. Les résultats appuient l'hypothèse, démontrant une plus grande variabilité de la connectivité occipito-temporale chez les PNV que les PV. De plus, chez les PNV, les connexions occipito-temporales qui variaient fortement à l'ER étaient aussi celles qui étaient le plus augmentées durant la tâche d'audition. Ceci suggère que la baisse de CF à l'ER est effectivement causée par l'appartenance du lobe occipital à plusieurs modes fonctionnels : les connexions liant à une région qui participe à une multitude de modes seront influencées par tous ces modes à l'ER, donc fortement diluées, mais aussi fortes que les autres lorsqu'un nombre restreint de modes est impliqué (p. ex. lors d'une tâche auditive).

Ensemble, les résultats de ce deuxième article résolvent le conflit apparent entre les études de CF à l'ER et les études d'activations, révèlent un aspect important de l'intégration fonctionnelle chez PNV et ajoutent un bémol aux études d'ER publiées sur ce sujet. Crucialement, les résultats mettent en évidence de nouvelles caractéristiques fonctionnelles du lobe occipital des PNV, notamment leur rôle dans un nombre important de modes fonctionnels. Ces effets étaient plus marqués pour les pôles occipitaux, un résultat qui s'accorde particulièrement avec le premier article de cette thèse qui démontrait que ces mêmes régions étaient subdivisées différemment chez les PNV.

Troisième article

Le troisième article de cette thèse s'accorde avec les deux premiers du fait qu'il présente une méthode qui permettra d'étudier les pôles occipitaux des PNV, cette région qui, selon les deux premiers articles de cette thèse, possédait des caractéristiques fonctionnelles fortement affectées par la cécité précoce. Cette méthode emploie des voix humaines, l'un des stimuli auditifs les plus pratiques à reconnaître chez l'humain, ce qui en fait l'un des plus pertinents

pour étudier la réponse des pôles occipitaux à des stimuli complexes. À cette fin, une méthode permettant de faciliter l'étude de ce phénomène a été développée. De plus, la méthode permettra de mieux comprendre les mécanismes implicites à la base de la perception de voix aussi bien chez les PV que les PNV, un phénomène encore inexploré chez ces derniers et incontournable si l'on veut comprendre l'origine de leurs suprap performances lors de tâches de perception vocale (voir la section : Futures pistes de recherche).

Le développement de cette nouvelle méthode était jugé nécessaire afin qu'une comparaison entre PNV et PV à l'aide d'imagerie fonctionnelle (électroencéphalographie, IRMf) ne soit pas biaisée par des différences de performances. Spécifiquement, des différences d'activations fonctionnelles entre deux groupes peuvent survenir lors d'une tâche si celle-ci n'est pas également difficile pour les populations testées (Fletcher et al., 1998; Perlstein et al., 2001). Considérant que les PNV possèdent des habiletés auditives accrues qui peuvent faciliter leur perception des voix, l'étude de ce phénomène à l'aide de méthodes d'imagerie requière un contrôle strict des performances. Donc, la méthode développée ici visait à mesurer la perception des voix afin de pouvoir en égaliser la difficulté. Comme le démontrent les résultats, ce but a été atteint puisque la méthode permet d'évaluer des paramètres nécessaires à l'obtention d'un certain niveau de difficulté chez chacun des participants.

En outre, la contribution théorique majeure de cet article est liée aux mécanismes cérébraux responsables de la perception de voix familières chez les PV. L'hypothèse principale de cet article portait sur le rôle de la connaissance de l'identité d'un locuteur et du type de stimuli entendus, dans la perception des voix familières. Il était postulé que les voix familières sont plus facilement perçues que les voix non familières même lorsqu'elles ne sont pas ouvertement reconnues et que cet effet persistait même lorsque les participants ne sont pas informés de la

présence de voix humaines durant l'expérience. Cette hypothèse découle des résultats de plusieurs études qui démontrent que l'analyse de la parole ou d'un discours est facilitée lorsque l'orateur est connu du participant (Newman & Evers, 2007; Nygaard et al., 1994; Nygaard & Pisoni, 1998; Pilotti et al., 2001; Souza et al., 2013; Yonan & Sommers, 2000). Pour tester l'hypothèse, des paires de sons contenant chacune une voix et une note de piano ont été présentées aux participants qui devaient départager lequel était un stimulus vocal. Ceci était fait en présence d'un bruit de masquage afin d'augmenter la difficulté de la tâche. Lors de la première expérience, les participants savaient que des voix leurs étaient présentées, mais pas que certaines étaient familières. Lors de la seconde, les participants ignoraient complètement que des voix leurs étaient présentées. La première hypothèse a été vérifiée et la seconde infirmée : les voix familières étaient plus faciles à discriminer des notes de piano que les voix inconnues, mais seulement lorsque les participants savaient que la moitié des stimuli était des voix. Ces résultats suggèrent que la mobilisation des populations neuronales impliquées dans la reconnaissance de voix familières est aidée par une activité anticipatoire qui est propre à une catégorie de sons. Ce type d'activité est observé lorsque les participants s'attendent à entendre une catégorie spécifique de sons et facilite la discrimination de ces derniers (Esterman & Yantis, 2010).

En conclusion, l'article fournit des indices sur les mécanismes impliqués dans l'analyse de voix familières et démontre la validité de la méthode qui y est développée. En outre, le succès de la méthode chez les PV et la possibilité de l'utiliser pour maintenir un certain de niveau de difficulté justifie son emploi lors d'études futures chez les PNV.

Localisation fonctionnelle : topographie des modules

La première étude de cette thèse révèle une caractéristique cruciale de la localisation fonctionnelle; elle démontre, de manière holistique, que la formation des modules fonctionnels « visuels » ne dépend que partiellement d'entrées sensorielles visuelles. Les études précédentes n'avaient encore jamais localisé de différences de topographies entre les modules fonctionnels des PNV et les PV. Afin d'expliquer ce phénomène, il a été suggéré que les modules se développent en fonction des propriétés intrinsèques des neurones qui les constituent ou de leurs connexions anatomiques (voir Ricciardi et al., 2014 pour une revue de ces hypothèses). Selon ces hypothèses, chez les PNV, la présence de modules n'ayant pas d'homologues avec ceux des PV résulterait de changements au niveau de ces propriétés.

Donc, si cette hypothèse est fondée, les pôles occipitaux des PNV, dont les modules ne sont pas les mêmes que chez les PV, présenteraient des neurones dont les propriétés diffèrent ou encore des entrées sensorielles fortement dissemblables à celles des PV. Il existe des données en faveur de ces deux points. Tout d'abord, chez les animaux aveugles, la morphologie et l'excitabilité des neurones composants le cortex « visuel » primaire sont différentes de chez les voyants (Bourgeois & Rakic, 1996; Izraeli et al., 2002; Laramée et al., 2011), modifiant leurs propriétés. En second lieu, V1 et V2 reçoivent des entrées non visuelles (Falchier et al., 2002; Karlen, Kahn, & Krubitzer; Laramée et al., 2011; Rockland & Ojima, 2003). De pair avec leur forte dépendance sur les entrées visuelles directes chez les voyants, la perte de vue engendrerait une dépendance sur ces autres entrées (Ptito, Moesgaard, Gjedde, & Kupers, 2005).

À l'opposé, les autres régions « visuelles » de bas niveau ne présentaient pas de différences topographiques. Ceci inclut l'aspect ventral des pôles occipitaux qui est impliqué dans l'analyse du braille chez les PNV (Amedi et al., 2003; Amedi et al., 2004; Sadato et al., 1996).

L'absence de différences topographiques suggère soit que les neurones composant cette région possèdent les propriétés nécessaires à analyser des stimuli de type Braille, ou encore qu'elles sont naturellement connectées à des régions impliquées dans ces processus. Dans ce cas précis, les résultats d'études chez les voyants appuient la première hypothèse en démontrant que, même chez les PV, le cortex visuel est impliqué dans des jugements tactiles (Merabet et al., 2004).

Bref, nos résultats originaux touchant la localisation fonctionnelle chez les PNV s'accordent non seulement avec les théories modernes expliquant le maintien des fonctions chez les PNV, ils leurs apportent aussi de nouvelles données qui, *a priori*, les renforcent.

Intégration fonctionnelle : connectivité fonctionnelle entre cortex sensoriels

L'apport majeur du deuxième article de cette thèse concerne la communication entre les différents cortex sensoriels chez les PNV, une caractéristique qui a influencé les théories récentes de la plasticité cérébrale. Spécifiquement, l'article démontre qu'une basse connectivité observée à l'ER chez les PNV n'est pas représentative de l'intégration fonctionnelle en place durant une tâche précise. Quoique seulement démontré pour une tâche auditive, il est envisageable, et même probable, qu'un phénomène semblable influence la CF entre les aires somatosensorielles et les lobes occipitaux. En effet, similairement à l'audition, les lobes occipitaux des non-voyants sont impliqués dans l'analyse tactile (Pietrini et al. 2004; Renier et al., 2010) tout en étant moins connectées aux aires somatosensorielles primaires (Burton et al., 2013; Liu et al., 2007; Yu et al., 2008).

Chez les PNV, la basse CF entre les différents cortex sensoriels et les lobes occipitaux supporte deux théories distinctes. Selon la première, les lobes occipitaux sont impliqués dans des phénomènes mnémoniques ou attentionnels chez les PNV plutôt que dans l'analyse des

sensations non visuelles (Burton et al., 2013). S'il est vrai qu'il existe une plus forte CF entre les lobes occipitaux et les aires frontales responsables de l'attention et du langage (Burton et al., 2013; Liu et al., 2007; Striem-Amit et al. 2015), il y a une autre explication à ce phénomène. Selon cette dernière, l'établissement des différents modes fonctionnels impliquant des lobes occipitaux dépendrait de processus attentionnels chez les PNV, ce qui expliquerait la plus grande CF entre ces régions (Bock & Fine, 2014). Cela n'exclut pas que certains modules occipitaux soient impliqués dans l'analyse du langage, la mémoire ou l'attention chez les PNV, mais généraliser cette idée à l'ensemble des lobes occipitaux serait fautif.

Selon une seconde théorie, la basse connectivité entre les cortex sensoriels et occipitaux indiquerait que les entrées sensorielles acheminées aux régions occipitales de bas niveau le sont par l'entremise de régions « visuelles » de haut niveau (Qin et al., 2013). Cette idée repose sur des données démontrant que la CF des PNV est plus basse que celle des PV seulement pour les régions « visuelles » de bas niveau. Toutefois, nos résultats démontrent que la CF occipito-temporale est augmentée plus fortement pour ces mêmes régions de bas niveau. Ceci met en doute la validité de cette théorie et suggère plutôt que seules les régions occipitales de bas niveau sont impliquées dans un plus grand nombre de modes fonctionnels chez les PNV.

Ainsi, nos résultats concernant l'intégration fonctionnelle chez les PNV ont un impact direct et important sur les théories portant sur le rôle des régions occipitales chez les PNV. Crucialement, ils démontrent la nécessité d'employer des mesures sensibles aux variations temporelles de la CF chez les PNV, une avenue de recherche qui n'avait jamais encore été explorée.

Pôles occipitaux chez les PNV : caractéristiques et fonctions

Les deux premiers articles de cette thèse mettent en évidence un changement important des propriétés fonctionnelles du lobe occipital des PNV, spécifiquement au sein des pôles occipitaux. Ensemble, les résultats de ces deux études suggèrent que le développement des pôles occipitaux dépend fortement de la présence d'entrées visuelles. Quoique les articles de cette thèse ne permettent pas d'établir la fonction des pôles occipitaux chez les PNV, elles pourraient être approximées à partir d'articles déjà parus, et qui ont examiné cette question, ou en étudiant les caractéristiques fonctionnelles des pôles occipitaux.

Pôles occipitaux : études sur la fonction des pôles occipitaux chez les PNV

Quel est le rôle des pôles occipitaux chez les PNV? Plusieurs articles ont examiné la question et deux propositions principales en ressortent.

La première proposition veut que les régions « visuelles » primaires et secondaires soient impliquées dans la lecture de braille ou l'analyse du langage. L'hypothèse est basée sur une série d'études qui démontrent que ces régions sont activées par des processus langagiers, ou encore que l'application de la SMT aux environs de la fissure calcarine vient perturber la lecture de braille (Amedi et al., 2003; Amedi et al., 2004; Cohen et al., 1997; Cohen et al., 1999; Sadato et al., 1996). Toutefois, parmi les études précédentes, celles qui permettent de visualiser les régions activées lors de l'analyse de ces stimuli (c.-à-d. employant la TEP ou l'IRMf) montrent que ce sont principalement les régions occipitales ventrales qui sont impliquées dans ces processus (Amedi et al., 2003, Cohen et al., 1999; Sadato et al., 1998; Bedny et al., 2011). Considérant que les régions différemment divisées chez les PNV se situaient plutôt au niveau

des pôles occipitaux dorsaux, il est peu probable que ces partitions soient celles qui sont impliquées dans le langage chez les PNV.

Selon la seconde proposition, les régions « visuelles » de bas niveau sont recrutées lors de tâches attentionnelles plutôt que par l'analyse de stimuli tactiles ou auditifs. L'opinion selon laquelle les PNV bénéficient d'habiletés attentionnelles accrues n'est pas nouvelle et a été démontrée plusieurs fois (Röder, Krämer, & Lange, 2007; Röder et al., 1999). Cependant, les résultats d'une étude d'activation ayant examiné spécifiquement cette question démontrent que la moitié antérieure de la fissure calcarine, non pas les pôles occipitaux, serait recrutée par ces processus (Weaver & Stevens, 2007). Cette proposition est supportée par des études récentes de connectivité qui démontrent que les PNV possèdent une plus forte CF entre la partie antérieure de la fissure calcarine et des régions frontales impliquées dans les processus attentionnels. Toutefois, cet effet n'est pas présent pour les régions postérieures, incluant les pôles occipitaux (Wang et al., 2013; Striem-Amit et al., 2015).

De pair avec les articles de cette thèse, les études démontrant l'implication des régions « visuelles » de bas niveau dans des processus langagiers ou attentionnels chez les PNV suggèrent que ces régions sont divisées en un minimum de trois grands modules fonctionnels, l'un antérieur-médian relié aux phénomènes attentionnels, un second ventral recruté par le langage ou la lecture de braille, et une troisième occupant l'aspect dorsal des pôles occipitaux. Quelles sont les fonctions de cette troisième région? La réponse est évasive. En effet, après une revue exhaustive des foci d'activations produits par une multitude de tâches et de stimuli variés, il ne semble pas y avoir de stimuli ou de tâches spécifiques qui activent précisément les pôles occipitaux dorsaux chez les PNV; lorsqu'ils sont activés, ils semblent l'être de manière non spécifique (Renier et al., 2010).

Pôles occipitaux : Caractéristiques chez les PNV

Bien que la majorité des études d'imagerie fonctionnelle chez les PNV ne mettent pas en évidence une fonction précise des pôles occipitaux dorsaux chez ces derniers, cela n'exclut pas que cette région possède une fonction encore méconnue. Afin d'émettre une hypothèse plausible sur cette fonction, il est nécessaire d'examiner les caractéristiques fonctionnelles de cette région. Ces dernières ont été mises en évidence par certaines études d'IRMf chez les PNV, par le deuxième article de cette thèse et par des études anatomiques chez les animaux aveugles. Ces études sont discutées ci-dessous.

À notre connaissance, seulement deux études d'IRMf démontrent des activations centrées sur l'aspect dorsal des pôles occipitaux chez les PNV. Cette différence d'activation entre les deux populations découlait de la présentation de stimuli auditifs et tactiles et n'était pas propre à la tâche effectuée (Renier et al., 2010; Park et al., 2011). Par exemple, dans leur étude, Renier et collègues ont présenté des notes de piano et des vibrations tactiles à leurs participants, ces derniers devaient soit localiser les stimuli, les identifier, ou détecter leur présence. Chez les PNV, chaque condition et sens (c.-à-d. audition et tact) menait à une activation des pôles occipitaux, cette activation n'était pas significativement différente entre les conditions. Cette non-spécificité de la réponse neuronale à différents sens et tâches pourrait expliquer pourquoi peu d'études chez les PNV montrent une activation de cette région. En effet, la majorité des études chez les PNV contrastent l'activation d'une tâche à celle d'une tâche contrôle. Si les pôles occipitaux sont activés de manière non spécifique, alors ce contraste viendrait masquer ces activations. L'aspect multisensoriel des régions visuelles de bas niveau est aussi supporté par plusieurs études chez les animaux énucléés dont le cortex « visuel »

répond à des stimuli auditifs et tactiles (Chabot et al., 2007; Izraeli et al., 2002; Kahn & Krubitzer, 2002; Karlen, Kahn, & Krubitzer 2006; Piché et al., 2007).

Cette observation s'accorde avec les résultats du deuxième article de cette thèse qui suggèrent que les pôles occipitaux sont impliqués dans un plus grand nombre de modes fonctionnels chez les PNV. Chez les PV, ces modes incluraient ceux impliqués dans l'analyse de stimuli visuels, tandis que chez les PNV, ils seraient composés de modes sous-tendant à la fois l'analyse auditive et l'analyse tactile. La modulation des connexions occipito-temporales par une tâche auditive supporte cette interprétation (deuxième article de cette thèse).

Les études anatomiques et fonctionnelles menées chez les animaux sont aussi indispensables à la caractérisation fonctionnelle des pôles occipitaux. En effet, elles dévoilent les voies par lesquelles les entrées tactiles et auditives sont acheminées à V1 et V2, ainsi que les rôles que ces entrées jouent chez les voyants. Plusieurs études, chez un nombre varié d'espèces animales, démontrent l'existence de connexions anatomiques directes entre les régions visuelles de bas niveau et les autres cortex sensoriels (opossums : Karlen, Kahn, & Krubitzer; primates : Falchier et al., 2002; Rockland & Ojima, 2003; souris : Laramée et al., 2011). Le rôle de ces connexions chez les voyants est particulièrement intéressant et pourrait éclairer leurs fonctions chez les non-voyants. Chez les premiers, tant animaux qu'humains, ces connexions supporteraient deux fonctions distinctes : l'intégration multisensorielle (Clemo et al., 2008; Falchier et al., 2002) et l'inhibition intersensorielle (Dehner, Keniston, Clemo, & Meredith, 2004). Ici, l'intégration multisensorielle consiste en l'apport d'informations non visuelles au lobe occipital afin de faciliter l'analyse de stimuli de différentes modalités qui coïncident temporellement et, donc, venant probablement d'une source unique (Hirokawa et al., 2008). À l'opposé, l'inhibition intersensorielle aurait pour but de réduire la distraction causée par des

stimuli conflictuels (Laurienti et al., 2002; Stein et al., 2002). Toutefois, ces connexions ne semblent pas suffisantes pour activer les neurones, et serviraient plutôt à en faciliter l'activation par des stimuli visuels (Clemo et al., 2008). Chez les animaux énucléés, l'inhibition est réduite, voire absente, menant à une excitation accrue des neurones recevant les fibres excitatrices (Izraeli et al., 2002). De pair avec des changements physiologiques des neurones de V2 (Bourgeois & Rakic, 1996; Laramée et al., 2011), cela faciliterait fortement l'activation des neurones par des entrées tactiles ou auditives.

Ensemble, les études décrites ci-dessus mettent en évidence plusieurs caractéristiques fonctionnelles et anatomiques des cortex « visuels » primaires et secondaires chez les PNV. Ces caractéristiques incluent une réponse aux stimuli tactiles et auditifs, des entrées provenant des cortex sous-tendant l'analyse de ces sens chez les PV et une facilitation de la réponse neuronale induite par ces connexions. Ainsi, il est possible d'élaborer certaines hypothèses sur les fonctions que pourraient avoir acquises ces régions suivant une privation visuelle précoce.

Pôles occipitaux : fonctions hypothétiques

Deux hypothèses principales sur les fonctions des pôles occipitaux dorsaux des PNV découlent des caractéristiques fonctionnelles et anatomiques de ces derniers.

Selon la première hypothèse, chez les PNV, les pôles occipitaux recevraient les entrées tactiles et auditives qui sont acheminées aux lobes occipitaux. Cette hypothèse a déjà été proposée auparavant par plusieurs études et revues de la littérature (Wittenberg et al., 2004; pour une revue de la littérature, voir : Kupers & Ptito, 2011; Kupers & Ptito, 2013; Merabet & Pascual-Leone, 2010; Ricciardi, Bonino, Pellegrini, & Pietrini, 2014). Les indices principaux en sa faveur sont l'existence de connexions anatomiques directes (ou même indirectes) entre les

cortex sensoriels primaires et secondaires, ainsi que l'excitabilité accrue des régions « visuelles » primaires. Ainsi, les entrées non visuelles peuvent être acheminées aux pôles occipitaux et leur présence est suffisante à l'activation de leurs neurones; une première étape nécessaire à leur analyse. Toutefois, les études qui avancent cette hypothèse s'abstiennent de spéculer ouvertement sur le rôle de ces activations au sein de l'ensemble des régions occipitales. Implicitement, il est suggéré que les pôles occipitaux servent de porte d'entrée aux stimuli non visuels et qu'ensuite l'information relative à ces sensations est redistribuée aux régions occipitales responsables d'une analyse complexe. En effet, les pôles ne sont pas les seuls à être activés par des stimuli tactiles et auditifs chez les PNV; il en est de même pour presque l'intégralité des lobes occipitaux. De plus, les connexions anatomiques permettant d'acheminer des entrées tactiles et auditives aux lobes occipitaux n'ont été observées qu'au niveau des aires visuelles primaires et secondaires (Cappe, Rouiller, & Barone, 2009), ainsi que pour quelques régions de plus haut niveau (Blank, Anwender, & von Kriegstein, 2011), laissant une large partie du cortex occipital sans entrées auditives ou tactiles directes. Donc, ces régions dépendent d'une autre source d'entrée, probablement les pôles occipitaux (mais voir Qin et al., 2013).

La seconde hypothèse est présentée dans le deuxième article de cette thèse et veut que les pôles occipitaux constituent un système permettant d'analyser différents stimuli en fonction des tâches à effectuer. Ce type de système a été mis en évidence par plusieurs articles chez les PV et est généralement nommé le « multiple demand system » (MDS; Duncan, 2010). Observé chez les primates et les humains, le MDS implique les lobes frontaux et est caractérisé par une forte adaptabilité de sa réponse à différents stimuli en fonction des demandes d'une tâche. Par exemple, les motifs d'activations du MDS encodent moins fortement les caractéristiques physiques des stimuli que leur pertinence au succès de la tâche (Sigala, Kusunoki, Nimmo-

Smith, Gaffan, & Duncan, 2008) : une même image ne recrutera le MDS de manière distincte que lorsqu'elle est nécessaire à l'accomplissement de la tâche effectuée par l'observateur (Downar, Crawley, Mikulis, & Davis, 2001; Everling, Tinsley, Gaffan, & Duncan, 2002). Cette caractéristique du MDS s'accorde avec les données qui démontrent que l'aspect dorsal des pôles occipitaux des PNV est activé de manière non spécifique par des stimuli variés (auditifs et tactiles), ainsi que par différentes tâches. De surcroît, afin d'accomplir sa fonction, le MDS doit nécessairement « interfacer avec plusieurs systèmes cérébraux séparés qui exécutent des opérations cognitives déterminées » (traduction libre de Duncan, 2010) et qui dépendront de la tâche effectuée. Cette modification en fonction de demandes passagères coïncide avec les résultats du deuxième article de cette thèse qui suggère que les pôles occipitaux des PNV font partie d'un nombre important de modes fonctionnels. Ensemble, ces résultats chez les PNV montrent des parallèles importants entre le MDS et les pôles occipitaux chez les PNV, suggérant que cette région pourrait supporter des fonctions semblables à celles soutenues par le MDS.

Futures pistes de recherche

Au cours des deux dernières décennies, l'étude des effets de la cécité sur la perception et l'organisation cérébrale a mené à une pléthore de découvertes importantes, mais plusieurs avenues de recherche restent inexplorées.

Le troisième article de cette thèse révèle l'une de ces pistes de recherche en démontrant l'existence de mécanismes implicites à la base de l'analyse des voix humaines chez les PV. Ce phénomène, encore inexploré chez les PNV, est pertinent à étudier chez ces derniers, car la perception de voix humaines est la principale méthode par laquelle ils peuvent identifier des gens et elle est la cible d'une plasticité intermodale et de la compensation sensorielle. En effet,

chez les PNV, la voix active non seulement les mêmes régions que chez les PV (le sulcus temporal supérieur), mais aussi une région visuelle : le gyrus fusiforme (Gougoux et al., 2009; Hölig et al., 2014) qui est dédié à l'analyse d'objets visuels tels les visages chez les PV (Kanwisher et al., 1997). Il a aussi été démontré que les PNV différencient plus facilement les voix (Bull et al., 1983; Braun, 2012) et qu'ils apprennent plus rapidement à les reconnaître (Föcker et al., 2012; Hölig et al., 2014). Considérant que les mécanismes implicites de la reconnaissance de voix facilitent l'analyse de la voix et de la parole, des habiletés qui sont aussi plus aiguisées chez les PNV (Bull et al., 1983; Hugdahl et al., 2004; Muchnik et al., 1991; Niemeyer & Starlinger, 1981), il est probable que ces mécanismes soient aussi affinés chez les PNV. Donc, il serait pertinent d'utiliser la tâche de discrimination de voix présentée dans le troisième article afin d'examiner les processus implicites de reconnaissance de la voix chez les PNV ainsi que pour vérifier que ce phénomène bénéficie aussi de la plasticité intermodale.

En outre, la démonstration de caractéristiques topographiques et fonctionnelles singulières au niveau du pôle occipital dorsal chez les PNV sollicite une exploration plus approfondie des fonctions de cette région afin de mieux en comprendre le rôle au sein de l'organisation cérébrale des PNV. Deux pistes supplémentaires semblent particulièrement pertinentes à examiner : la non-spécificité de la réponse de cette région et les caractéristiques qu'elle encode.

La première piste d'investigation concerne la non-spécificité de la réponse neuronale des pôles occipitaux à des modalités sensorielles non visuelles. Ainsi, il serait important de s'assurer que cette région est réellement activée à la fois par des stimuli tactiles et des stimuli auditifs. De plus, il faut établir si cette non-spécificité s'étend aux assemblées neuronales composant cette région du lobe occipital. En effet, il a été démontré que plusieurs réseaux locaux possédant leurs

propres fonctions peuvent se chevaucher (Peelen & Downing, 2007). En apparence, ces modules cérébraux sembleraient impliqués de manière non spécifique dans les fonctions de chacune des assemblées neuronales sans pour autant les distinguer. Autrement dit, la prétendue non-spécificité des pôles occipitaux dorsaux à l'audition et au tact pourrait résulter d'un chevauchement de réseaux neuronaux locaux, l'un impliqué dans l'analyse tactile et l'autre dans l'analyse auditive. Cette distinction est importante afin de mieux comprendre la fonction de ces régions au sein des autres modules, apparemment plus spécialisés, du lobe occipital (Collignon et al., 2011). Les réponses à ces questions peuvent aisément être obtenues en utilisant des paradigmes d'adaptation qui ont été développés précisément afin d'examiner les propriétés fonctionnelles de populations neuronales se chevauchant (Grill-Spector & Malach, 2001).

Deuxièmement, il est désirable d'étudier les caractéristiques des stimuli qui sont encodées par l'aspect dorsal des pôles occipitaux. Ces dernières pourraient être génériques et ne servir qu'à faciliter l'analyse de stimuli d'une manière similaire à certaines régions occipitales impliquées dans l'intégration multisensorielle (Hirokawa et al., 2008). À l'opposé, les pôles occipitaux dorsaux pourraient encoder certaines caractéristiques physiques des stimuli telle la fréquence des sons, un phénomène observé chez des cellules des aires visuelles primaires et secondaires de rats aveugles (Izraelli et al., 2002; Piché et al., 2007), ou encore des éléments plus complexes. Afin de départager ces possibilités, il serait nécessaire d'évaluer la réponse de ces régions à des stimuli simples (ex. vibrations tactiles, tons purs) et complexes (ex. textures, voix et sons musicaux). Grâce à la méthode du troisième article de cette thèse, il serait possible de s'assurer que les différences putatives (entre les types de stimuli et les groupes) ne soient pas causées par des différences de performances sur les tâches (Perlstein et al., 2001). Ici, l'utilisation de stimuli complexe ne vise pas à déterminer s'il existe une réponse préférentielle

à ces stimuli au sein des pôles occipitaux, mais plutôt à vérifier que ces derniers peuvent influencer l'encodage des assemblées neuronales s'y trouvant. En effet, il est démontré que les régions sensorielles primaires et secondaires peuvent moduler leurs réponses en fonction des demandes externes, menant à une représentation des stimuli complexes (Bonte et al., 2014; Formisano et al., 2008; Huk & Heeger, 2000; Li, Piëch, & Gilbert, 2004). Vérifier que ce type de processus est encore présent chez les PNV est indispensable afin de comprendre l'influence qu'a la cécité sur cette région du cortex et d'en saisir la fonction chez les PNV. Ceci peut être accompli en analysant des données d'IRMf à l'aide de motifs multivoixels (multi-voxel pattern analysis; MVPA; voir Formisano et al., 2008 pour une application à ce type de questions).

Conclusion

Le fonctionnement macrométrique du cerveau humain dépend de deux principes fondamentaux : la localisation fonctionnelle et l'intégration fonctionnelle. Ainsi, chaque zone du cerveau effectue des opérations qui sont influencées par d'autres régions cérébrales et qui les influencent en retour. L'impact de la vision (ou de son absence) sur l'établissement de ces réseaux fonctionnels a connu un engouement récent et il a été démontré que le lobe occipital des personnes atteintes de cécité précoce ou congénitale maintient généralement ses caractéristiques fonctionnelles.

Globalement, les articles de cette thèse révèlent des caractéristiques inédites de l'organisation fonctionnelle du cerveau des personnes non-voyantes. Ces observations mettent non seulement en doute certaines théories concernant la plasticité cérébrale chez les non-voyants, elles fournissent des données novatrices qui permettent de mieux comprendre ce phénomène. Crucialement, les articles révèlent l'existence, au sein des pôles occipitaux, de modules dont les

caractéristiques fonctionnelles sont encore méconnues et qui n'ont jusqu'à maintenant jamais été sujets à une étude directe. Ainsi, les caractéristiques dévoilées par ces expériences pavent la voie vers de nouvelles hypothèses et études qui permettront d'approfondir notre conception du cerveau et de la plasticité cérébrale.

En conclusion, si la question des habiletés des personnes non-voyantes a débuté comme débat philosophique, elle a su aviver la curiosité des chercheurs durant plusieurs siècles, dont la mienne, et nous permet maintenant d'étudier des aspects importants du développement cérébral.

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