UNIVERSITE CLAUDE BERNARD - LYON 1

FACULTE DE MEDECINE ET DE MAIEUTIQUE LYON-SUD CHARLES MERIEUX

Année 2016 N°

DÉFICITS AUDITIFS APRÈS UN ACCIDENT VASCULAIRE CÉRÉBRAL : PERCEPTION, MÉMOIRE ET ÉMOTIONS MUSICALES

Thèse

Présentée à l'Université Claude Bernard -Lyon 1

et soutenue publiquement le 7 octobre 2016

pour obtenir le grade de Docteur en Médecine

par Mme HIREL Catherine

Née le 27 Février 1987 à Versailles

Président du jury : Pr Norbert NIGHOGHOSSIAN

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Le Serment d'Hippocrate

Je promets et je jure d'être fidèle aux lois de l’honneur et de la probité dans l'exercice de la Médecine.

Je respecterai toutes les personnes, leur autonomie et leur volonté, sans discrimination.

J'interviendrai pour les protéger si elles sont vulnérables ou menacées dans leur intégrité ou leur dignité. Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences. Je ne tromperai jamais leur confiance.

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Résumé

But de l'étude : Les déficits auditifs survenant après un accident vasculaire cérébral (AVC) peuvent concerner le traitement du langage et/ou de la musique, entraînant une aphasie et/ou une amusie. L'objectif de ce travail était de déterminer les déficits musicaux pouvant survenir après un AVC, en étudiant la perception musicale, la mémoire à court terme auditive verbale et musicale, et les émotions musicales.

Matériels et méthodes : Des patients avec un infarctus dans le territoire de l'artère cérébrale moyenne gauche (n=10) et droite (n=10) et des sujets contrôle (n=14) ont été testés avec un bilan neuropsychologique incluant les fonctions cognitives globales et le langage. Tous les participants ont ensuite réalisé une tâche de perception musicale (MBEA), une tâche de mémoire à court terme (MCT) auditive verbale et musicale, et une tâche de catégorisation des émotions musicales et faciales, avec cotation de l'intensité des émotions. Tous les participants ont bénéficié d'une IRM cérébrale et une analyse en Voxel-based Lesion Symptom Mapping (VLSM) a été réalisée pour la tâche de MCT auditive.

Résultats : Trois patients présentaient une amusie acquise. Les patients avaient des performances moins bonnes que les sujets contrôle pour la tâche de mémoire à court terme, quelque soit la modalité (verbale, musicale, visuelle) et la latéralisation de la lésion. Les résultats individuels montraient une double dissociation entre certains patients présentant un déficit de MCT auditive verbale, sans déficit de MCT auditive musicale, et inversement. Les analyses en VLSM suggéraient que la voie dorsale est impliquée dans la MCT verbale, musicale et visuelle, alors que la voie ventrale est impliquée dans la MCT musicale. Les performances pour la tâche de catégorisation des émotions musicales étaient significativement plus faibles chez les patients avec des lésions de l'hémisphère gauche, en comparaison avec les sujets contrôle. Les patients avec des lésions de l'hémisphère droit cotaient l'intensité des émotions musicales plus faiblement pour la tristesse et la peur que pour la joie et la sérénité. Il n'y avait pas de différence pour les émotions faciales (catégorisations et intensité) entre les patients et les sujets contrôle. Enfin, nous rapportons un cas d'amusie acquise associée à une anhédonie musicale, après un infarctus temporal droit.

Conclusion : Les déficits auditifs après un AVC sont variés et peuvent s'associer. Les troubles concernant la musique devraient être dépistés par des tests neuropsychologiques validés, pour pouvoir proposer des techniques de rééducation.

Summary

Goal of the study: Auditory cognitive deficits after stroke may concern language and/or music processing, resulting in aphasia and/or amusia. The aim of this work was to assess the potential musical deficits after stroke, by studying musical perception, auditory short-term memory for verbal and musical material, and musical emotions.

Material and methods: Patients with an ischemic stroke in the right (N=10) or left (N=10) middle cerebral artery territory and matched control participants (N=14) were tested with a detailed neuropsychological assessment including global cognitive functions and language tasks. All participants then performed a musical perception task (MBEA), a verbal and musical auditory short-term memory (STM) tasks, and a task of categorization of musical and facial emotions, and rating the intensity of the emotions. All participants had a MRI and a Voxel-based Lesion Symptom Mapping (VLSM) analyses has been performed for the STM tasks.

Results: Three patients had an acquired amusia. Patients had lower performance for the STM tasks in comparison with control participants, regardless of the material (words, tones, visual) and the lesion side. The individual patient data showed a double dissociation between some patients exhibiting verbal deficits without musical deficits or the reverse. Exploratory VLSM analyses suggested that dorsal pathways are involved in verbal, musical, and visual STM, while the ventral auditory pathway is involved in musical STM. Performance in the musical emotion recognition test was found to be significantly lower in patients with left lesions in comparison with control participants. Patients with right lesions rated the emotional intensity of music lower for sadness and fear than for joy and serenity. There was no difference for faces emotions (categorization or intensity) between patients and control participants. We reported one case report of acquired amusia associated with musical anhedonia, after right temporal infarction.

Conclusion: Auditory deficits after stroke are various and can associate. Those concerning music should be detected by validated neuropsychological assessment, to propose reeducation.

Abbréviations

AVC: Accident Vasculaire Cérébral

fMRI: Functional MRI

IRM: Imagerie par Résonnance Magnétique

MBEA: Montréal Battery of Evaluation of Amusia

MCT: Mémoire à Court Terme

MEC: Montreal Evaluation de la Communication

MEG: Magneto-encephalography

MMSE: Mini Mental State Examination

MoCA: Montreal Cognitive Assessment

MRI: Magnetic Resonance Imaging

PDT: Pitch Discrimination Threshold

PET: Positron Emission Tomography

RHH: Right Hemisphere Hypothesis

STM: Short Term Memory

VBM: Voxel Based Morphometry

VH: Valence Hypothesis

VLSM: Voxel-based Lesion Symptom Mapping

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I. Introduction

Les accidents vasculaires cérébraux (AVC) sont la deuxième cause de mortalité dans le monde et la première cause de handicap. La rééducation motrice est largement développée, avec de nombreuses études montrant son efficacité sur la dépendance après un AVC. Cependant, les séquelles neuropsychologiques après un AVC ont aussi de lourdes conséquences sur la vie sociale, personnelle et professionnelle des patients. Elles peuvent nuire à la récupération fonctionnelle et la qualité de vie. Pourtant, la rééducation cognitive est beaucoup moins développée. Le diagnostic de ces atteintes cognitives est insuffisamment fait, et nécessite la réalisation d'un bilan neuropsychologique complet comprenant des tests validés. Le "Mini Mental State Examination" (MMSE) et le "Montreal Cognitive Assessment" (MoCA) sont deux tests de dépistage largement utilisés en clinique dans les unités neuro-vasculaires et permettent d'orienter certains patients vers un bilan neuropsychologique plus précis (1,2). Cependant ces tests ont été développés pour diagnostiquer des démences d'origine neuro-dégénérative et ne permettent pas de détecter des atteintes cognitives spécifiques de lésions vasculaires focales.

Ces déficits cognitifs surviennent précocement après l'AVC (3). Ils sont même parfois le seul symptôme à la phase aiguë. Le profil cognitif de patients irlandais à 6 mois d'un AVC a été étudié (ASPIRE-S). 56,6% des patients avaient un déficit cognitif (évalué avec la MoCA), les femmes et les patients avec des antécédents cardio-vasculaires étant les plus à risque (4). Deux autres études basées sur le MMSE montraient que 32% des patients avaient un déficit cognitif 3 ans après l'AVC (5), et 21% 14 ans après l'AVC (6). Après un AVC peut également s'installer progressivement un déclin cognitif pouvant mener à une démence vasculaire (7). De manière plus subtile, de nombreux déficits neuropsychologiques peuvent survenir au moment de l'AVC, alors même que le patient ne présente pas de signe de démence sur les tests des fonctions cognitives globales (MMSE, MoCA). Par exemple, certains patients remarqueront une diminution de leurs performances intellectuelles au moment de la reprise de leur travail après l'AVC. Ces déficits neuropsychologiques peuvent impliquer de nombreux domaines : la mémoire, l'attention, les fonctions visuo-spatiales, les fonctions exécutives, le langage...

Dans ce travail de thèse, nous nous sommes plus particulièrement intéressés aux déficits cognitifs touchant l'audition, et notamment la musique, après un AVC.

A. Musique et langage après un AVC

La musique et le langage sont présents dans toutes les sociétés humaines. La musique n'est pas indispensable à la survie ou à la reproduction de l'espèce mais elle procure un bénéfice important sur notre bien-être physique et moral. On sait maintenant que le traitement de la musique met en jeu les deux hémisphères cérébraux, avec une préférence de l'hémisphère gauche pour le traitement du rythme, de la représentation sémantique de la musique (identification et reconnaissance des mélodies) et une préférence de l'hémisphère droit pour la perception mélodique (hauteur, contour) et le timbre (distinction de différents instruments de musique) (8–11). Cette meilleure compréhension du cerveau musical a été possible notamment grâce à des études chez des patients cérébro-lésés (accident vasculaire cérébral ou lobectomie pour épilepsie réfractaire).

Dans le domaine auditif, les troubles les mieux documentés et testés en pratique clinique concernent la perception et la production du langage. Néanmoins, les lésions cérébrales, notamment temporales ou frontales, peuvent être associées à des plaintes auditives ne concernant pas, ou pas uniquement, le langage, et pouvant avoir des répercussions sociales souvent sous-estimées. Les plaintes les plus fréquentes concernent les agnosies auditives, déficit de reconnaissance des sons complexes, pouvant concerner le langage et/ou la musique (12).

Les troubles du langage (aphasie) sont plus fréquents lors de lésion de l'hémisphère gauche (dominant chez les droitiers), alors que les troubles musicaux (amusie) surviennent lors de lésions droite ou gauche (13). Cependant, l'amusie semble plus fréquente et plus sévère lors de lésions de l'hémisphère droit. L'agnosie musicale et l'agnosie des sons de l'environnement sont des troubles dissociés (14). Ces atteintes ne sont pas recherchées de manière systématique à l'interrogatoire et sont largement sous-estimées. En effet, dans une étude, 60 % des patients étaient amusiques à une semaine d’un AVC dans le territoire de l’artère cérébrale moyenne et 42% le restaient à 3 mois (13).

L'amusie est définie comme une agnosie auditive consécutive à une lésion cérébrale ou d’origine congénitale. Elle s’exprime selon plusieurs modalités : amusie réceptive ou expressive, alexie musicale, amnésie musicale ou instrumentale, agraphie musicale, troubles du rythme (15). Le test validé pour la détection de l'amusie, qu'elle soit congénitale ou acquise, est le MBEA (Montreal Battery of Evaluation of Amusia, (16)), qui comprend 6 sous-tests (tonalité, contour mélodique, intervalle de hauteurs, rythme, métrique, mémoire). Cependant, ce test n'est utilisé que dans le cadre de la recherche et pas en pratique clinique.

Les résultats des études de neuropsychologie chez les patients cérébro-lésés, ainsi que les données de neuro-imagerie chez le sujet sain, ont conduit à considérer les traitements de la musique et du langage comme reposant au moins en partie sur des réseaux cérébraux séparés (hypothèse de modularité, (17)). Néanmoins, les troubles langagiers et musicaux peuvent co-exister. L'amusie acquise après un AVC est souvent associée sur le plan cognitif à un déficit de la mémoire de travail et de l'apprentissage, des fonctions exécutives et visuo-spatiales et du langage (13). Les patients amusiques avaient de moins bons résultats sur les tests d'expression verbale et de compréhension que les patients non amusiques.

Les études sur l'amusie congénitale ont également permis d'avancer des hypothèses sur les réseaux neuronaux impliqués dans le traitement de la musique, et leurs liens éventuels avec les régions cérébrales responsables du traitement du langage. L'amusie congénitale (18) est présente chez 2-4% de la population et a fait l'objet de nombreuses recherches ces dernières années. Sur le plan anatomo-fonctionnel, il a été montré grâce à une étude en VBM ("Voxel Based Morphometry") que les amusiques congénitaux présentent une diminution de la substance blanche et une augmentation de la substance grise dans le gyrus frontal inférieur droit par rapport à des sujets contrôle (19). Une étude en tractographie a montré qu'il y avait une diminution du nombre de fibres du faisceau arqué à droite chez les amusiques congénitaux (20). Une étude en magnétoencéphalographie a également montré que les réseaux fronto-temporaux bilatéraux sont impliqués (21). Les amusiques congénitaux reconnaissent et traitent la parole, la prosodie linguistique et les sons de l'environnement aussi bien que les sujets contrôles (18).

Chez les patients cérébro-lésés, selon la localisation de la lésion, il pourrait donc exister un déficit dans le traitement auditif du langage en cas de lésion de l'hémisphère gauche, et un déficit dans le traitement de la musique en cas de lésion de l'hémisphère droit ou gauche, l'hypothèse étant celle de réseaux neuronaux dissociés entre langage et musique, mais situés dans des régions proches.

B. Objectifs de la thèse : Perception, Mémoire et Emotions musicales après un AVC

L'objectif de ce travail de thèse était de mieux caractériser les troubles musicaux pouvant survenir après un AVC, en étudiant la perception musicale, la mémoire à court terme auditive et les émotions musicales. L'analyse de la littérature montre que l'objectivation d'une amusie ou d'une aphasie repose sur des tests neuropsychologiques relativement différents. Pour une meilleure compréhension des troubles auditifs de haut niveau après une lésion cérébrale, il est donc souhaitable d'objectiver les troubles musicaux et langagiers dans un cadre méthodologique commun. Un des objectifs de ce travail était d'étudier les réseaux cérébraux impliqués dans le traitement du langage et de la musique, chez des patients cérébro-lésés, grâce à un paradigme commun. Pour cela, nous avons étudié la mémoire à court terme (MCT) auditive.

La mémoire à court terme permet le stockage des informations sensorielles (ici auditives) pendant un temps limité. La capacité de la mémoire à court terme auditive verbale peut se mesurer avec le test du « digit span » (empan de chiffres), celle-ci se situe entre 5 et 9 items. Chez les sujets sains, les mécanismes de mémoire à court terme auditive pour les mots, les notes et le timbre sont différents (22). Dans l'amusie congénitale, un trouble sélectif de la mémoire à court terme des mélodies et du timbre a été mis en évidence, alors que la mémoire à court terme verbale est intacte (23). Chez les patients présentant une lésion ischémique cérébrale, on observe que le gyrus temporal supérieur et postérieur gauche est impliqué dans la capacité de mémoire à court terme auditive verbale (24), ainsi que les aires pariétales inférieures gauches (25). Nous avons donc choisi d'inclure les patients ayant présenté un accident ischémique cérébral dans les régions pariéto-fronto-temporales (territoire de l'artère cérébrale moyenne), régions fortement impliquées dans le traitement auditif du langage et de la musique.

En plus de l'étude de la perception musicale et de la mémoire à court terme auditive après un AVC, nous nous sommes aussi intéressés aux émotions. En effet, la cognition musicale est toujours accompagnée d'une réponse émotionnelle. On sait que l'écoute de la musique active des structures bien au-delà du cortex auditif, telles que les aires frontale, temporale, pariétale, les régions limbiques et para-limbiques. Ces régions sont impliquées dans l'attention, la mémoire de travail, la mémoire épisodique et sémantique mais aussi les émotions. L'écoute d'une musique procurant une émotion intense active les mêmes aires

cérébrales impliquées dans les émotions liées par exemple à la consommation de nourriture, au sexe, et à la consommation de drogue chez des sujets dépendants (26). Ces émotions sont fondamentales pour la fonction sociale de la musique.

Il semble que les émotions musicales et la perception musicale sont relativement dissociées. Des cas de patients cérébro-lésés présentant une anhédonie musicale sans trouble perceptif ont été décrit dans la littérature (27,28). Il existe également de nombreux cas d'amusie acquise sans anhédonie. Nous rapportons ici le cas d'un patient présentant une amusie acquise associée à une anhédonie musicale dans les suites d'un infarctus temporal droit (29). Les amusiques congénitaux présentent des difficultés de catégorisation des émotions musicales mais leur ressenti émotionnel reste relativement intact (30). Des patients ayant bénéficié d'une lobectomie temporale unilatérale dans le cadre d'une épilepsie pharmaco-résistante présentaient un déficit de reconnaissance des musiques évoquant la peur. Des études ont montré un déficit de reconnaissance des émotions faciales chez des patients ayant présenté un AVC (31–33).

Sur le plan clinique, le bilan neuropsychologique habituel post-AVC teste classiquement le raisonnement, les fonctions exécutives, la mémoire, l'attention, les capacités visuo-spatiales et le langage. Il est orienté par les plaintes du patient. Nous proposons ici d’évaluer l’intérêt de tester la perception musicale, la mémoire à court terme auditive et les émotions musicales dans le bilan neuropsychologique, en fonction de la plainte des patients. Les résultats de cette étude permettraient d’orienter les choix des techniques de rééducation en fonction du type d'atteinte (34).

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II. *Article 1 : "Verbal and musical short-term memory: Variety of auditory disorders after stroke"

Title: Verbal and musical short-term memory: Variety of auditory disorders after stroke

Authors: Catherine Hirel[1, 2, 3, 4], Norbert Nighoghossian[3, 4, 5], Yohana Lévêque[1, 2, 3], Salem Hannoun[3, 5], Lesly Fornoni[1, 3], Sébastien Daligault[6], Patrick Bouchet[1, 3], Julien Jung[1, 3, 4], Barbara Tillmann[2, 3], and Anne Caclin[1, 3]

Affiliations:

[1] INSERM, U1028, Lyon Neuroscience Research Center, Brain Dynamics and Cognition Team, Lyon, F-69000, France;

[2] CNRS, UMR5292, Lyon Neuroscience Research Center, Auditory Cognition and Psychoacoustics Team, Lyon, F-69000, France;

[3] University Lyon 1, Villeurbanne, F-69000, France;

[4] Stroke Department, Hospices Civils de Lyon, Hôpital Neurologique Pierre Wertheimer, Bron, F-69000, France;

[5] CREATIS, CNRS, UMR5220; INSERM, U1044, University Lyon 1, F-69000, France;

[6] CERMEP, MEG Department, Bron, F-69000, France.

Corresponding author: Catherine Hirel; e-mail : cat.hirel@gmail.com; address: INSERM U1028, Centre de Recherche en Neurosciences de Lyon, Equipe Dynamique Cérébrale et Cognition, Centre hospitalier le Vinatier, Bâtiment 452, 95 Bd Pinel, Bron, F-69500, France.

Abstract:

Auditory cognitive deficits after stroke may concern language and/or music processing, resulting in aphasia and/or amusia. The aim of the present study was to assess the potential deficits of auditory short-term memory for verbal and musical material after stroke and their underlying cerebral correlates with a Voxel-based Lesion Symptom Mapping approach (VLSM). Patients with an ischemic stroke in the right (N=10) or left (N=10) middle cerebral artery territory and matched control participants (N=14) were tested with a detailed neuropsychological assessment including global cognitive functions, music perception and language tasks. All participants then performed verbal and musical auditory short-term

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memory (STM) tasks that were implemented in the same way for both materials. Participants had to indicate whether series of four words or four tones presented in pairs, were the same or different. To detect domain-general STM deficits, they also had to perform a visual STM task. Behavioral results showed that patients had lower performance for the STM tasks in comparison with control participants, regardless of the material (words, tones, visual) and the lesion side. The individual patient data showed a double dissociation between some patients exhibiting verbal deficits without musical deficits or the reverse. Exploratory VLSM analyses suggested that dorsal pathways are involved in verbal (phonetic), musical (melodic), and visual STM, while the ventral auditory pathway is involved in musical STM.

A. Introduction

1. Auditory deficits after stroke

Music and language are present in all human societies. Even though music is not essential for the survival or the reproduction of the human race, it provides benefits for our physical and moral well-being (1). Auditory cognitive deficits after stroke may affect language and/or music processing (2,3), and can also impact the processing of environmental sounds (4). Aphasia is more frequent after lesions in the left hemisphere, whereas acquired amusia can appear after lesions in both left or right hemispheres (3). Amusia is a music agnosia characterized by the inability to recognize music in the absence of sensory, intellectual, verbal and mnesic impairments. Amusia is rarely documented after stroke and remains largely underestimated. In a study, 60% of patients had acquired amusia one week after stroke in the territory of the middle cerebral artery, and 42% remained amusic three months after stroke (3). In another study, 69% of the stroke patients (tested ten days after stroke) had deficits in perceptual musical functions, whatever the lateralization of the lesions in frontal, temporal and parietal areas (5). Acquired amusia may be also associated with musical anhedonia (6), a loss of pleasure in listening to music, which can also arise without any perceptual deficits (7,8).

After brain damage, music and language deficits do not always co-occur, as evidenced by reported cases of amusia without aphasia (or the reverse) (9–12). These reported double dissociations suggest that music and language are processed by (at least partly) separate cerebral networks. However, the diagnosis of amusia or aphasia relies on qualitatively different neuropsychological testing: Diagnosing aphasia typically involves tests of language

comprehension and production, whereas diagnosing amusia relies on testing the perception of various musical dimensions (e.g., pitch, rhythm) or musical emotions. To allow for a better understanding of auditory deficits after brain damage, music and language disorders needs to be assessed with the same methodological approach. For this aim, our present study tested patients' short-term memory (STM) for auditory material (either verbal or musical) in comparison to visual material with the same experimental paradigm. STM is a basic cognitive ability involved in a wide range of tasks and contexts, and deficits in STM could be associated to or cause various patterns of deficits (see for example (13), for a discussion of how deficits in pitch STM might be central in congenital amusia).

2. Auditory short-term memory: behavior and cerebral correlates

Auditory verbal STM refers to a temporary memory store of verbal information for a short period of time (on the order of seconds). Baddeley's model (14) posits that auditory verbal working memory has two components: a phonological store, for very brief storage of verbal information, and an articulatory rehearsal component (phonological loop), for refreshing the information and keeping it active. Previous research investigating brain-damaged patients suggests that the left inferior parietal lobe is critical for the phonological store and the left inferior frontal lobe for the articulatory rehearsal component (15–17).

A Voxel-based Lesion Symptom Mapping (VLSM) study on stroke patients showed that auditory verbal STM is linked to the left middle temporal gyrus, left superior temporal gyrus (including Heschl's gyrus) and left inferior parietal areas (angular gyrus and supramarginal gyrus) (18). An analysis of the lesions of patients with conduction aphasia highlights the importance of a region in the posterior portion of the left planum temporale, area Spt (Sylvian-parietal-temporal) for phonological STM (19). More generally, the area Spt is a sensory-motor integration area for vocal tract actions (20).

Functional Magnetic Resonance Imaging (fMRI) and Positron Emission Tomography (PET) studies with healthy participants showed that the left supramarginal gyrus is involved in short-term storage of phonological information (21–23). They further suggest that a larger network of cortical areas is operating in verbal STM, including the auditory cortex (notably left superior temporal areas), the (left) premotor cortex, and Broca's area, which supports the articulatory processes.

Taken together, the studies with brain-damaged patients and the neuroimaging studies in healthy participants converge on the implication of temporal posterior, parietal inferior, and

frontal inferior regions in auditory verbal STM, with a predominant role for left-hemisphere structures.

In comparison to verbal material, the cerebral correlates of STM processing for tonal (musical) material have been less investigated by neuropsychological and neuroimaging studies. A study on brain-damaged patients (lobectomy for intractable epilepsy) showed that patients with right fronto-temporal lesions had a deficit in the retention of pitch in STM (24). To our knowledge, no research has investigated the anatomical locus of auditory musical STM in stroke patients.

A PET study in healthy participants showed that blood flow increased in the posterior superior temporal lobe, inferior frontal regions and the cerebellum when participants compared pitch sequences of six tones (requiring a same/different judgment), a classical STM paradigm (25). The network was bilateral, but predominant in the right hemisphere. Using fMRI when participants performed a STM task with single tones, Stevens et al. showed bilateral activation in the supra-marginal gyrus, the posterior insula and the posterior inferior temporal gyrus as well as activation in the right IFG (26). Grimault et al. showed in a MEG study the implication of superior parietal lobe and pre-central gyrus bilaterally in STM for tones (27). Other functional imaging studies showed the implication of bilateral parieto-fronto-temporal areas in pitch STM tasks (26,28–30), while a tDCS study suggested a causal involvement of the left SMG in non-musicians (31).

Some data sets suggest (at least partly) separate cognitive and neural resources for verbal and musical STM. In control participants, auditory STM seems to be different for words, tones and timbre. In congenital amusia, a selective disorder of auditory STM for tones and timbre has been demonstrated, while verbal STM is intact (13,32). The disorder of auditory STM for tones has been confirmed with tonal and atonal sequences, contrasting with normal performance for the verbal digit span (33). For a musical STM task, functional anomalies in a bilateral fronto-temporal network have been reported with MEG data for congenital amusia (34), supporting the view that this fronto-temporal network is involved in non-verbal auditory memory.

The work on congenital amusia thus suggests that the processing and storage of musical stimuli might recruit, at least partly, a different sub-system of STM than speech. However, neuroimaging studies on control participants have uncovered a cortical network for tonal STM that was surprisingly similar to the network for verbal STM (35,36). The present study with stroke patients might thus further shed light on whether common or separated

neural resources are involved in verbal and musical STM. Furthermore, whereas in congenital amusia compensatory plastic changes over the course of development in infancy might account for normal performance in verbal STM, such plastic changes should be largely reduced in the adult patient population tested here.

3. Objectives of the present study

Our present study investigated memory deficits after stroke, in particular verbal and musical auditory STM (in comparison to visual STM), and the cerebral underpinnings of these deficits using an exploratory voxel-based lesion symptom mapping approach. We included patients with focal cortical lesions in regions of interest for auditory STM, i.e., temporo-parieto-frontal areas in the territory of the middle cerebral artery.

B. Materials and methods

1. Participants

Twenty patients and fourteen control participants were included in the present study. Stroke patients were recruited from the stroke unit of the neurological hospital in Lyon, France. The main inclusion criterion was the presence of an ischemic stroke in the right or left middle cerebral artery territory, confirmed by MRI. Inclusion criteria also included: age over 18 years, native French-speakers, no other prior neurological or psychiatric disease, no severe cognitive disorder, no severe hearing loss, being able to have an MRI scan and to be tested with various behavioral tests for 2 hours. Patients were all tested in the chronic phase of their stroke (4-52 months after stroke). The same inclusion criteria (except criteria related to stroke) were applied to control participants, which were matched to the patients for age, gender, education level and music training. All participants gave written consent. The study was approved by the appropriate French ethics committee on Human Research (CPP Sud-Est III, 2014-050B).

2. Neuropsychological assessment

The behavioral measures (audiometry, neuropsychological assessment, STM tasks, and other behavioral tasks beyond the scope of the present report) were run during two sessions of approximately two hours each. Standard audiometry was performed to exclude severe hearing loss. Series of neuropsychological measures were performed to assess general cognitive abilities (MMSE, Mini Mental State Examination, (37)) and language deficits, including tests of lexical and categorical verbal fluencies and a short battery of denomination (BARD, (38)).

Music cognition was evaluated as part of the neuropsychological assessment with the MBEA (Montreal Battery of Evaluation of Amusia, (39)). The MBEA includes six subtests that measure different components of music cognition. The scale, contour, interval and rhythm subtests comprise 30 pairs of piano melodies, and participants have to judge, on each trial, whether the two melodies are the same or different. In the metric subtest, participants had to categorize melodies as either a waltz or a march and in the memory subtest they had to determine if the melody has been heard during previous trials or not. For each subtest, the maximum score was 30. The MBEA score was calculated as the mean score of the six subtests. This test allowed us to diagnose acquired amusia after stroke.

We also evaluated participants' pitch discrimination thresholds, using a two-alternative forced choice task with two-tone pairs in an adaptive paradigm (32).

3. Short-term memory tasks

Verbal and musical auditory STM performance was measured using delayed matching-to-sample tasks (32). Participants listened to an auditory sequence (S1), which consisted of four events (words or tones), followed by a 1-sec silence, and then a second sequence (S2), in which the four events were the same or different from S1. If the second sequence was different, only one event was changed (i.e., a new word/tone was introduced). The change never occurred in the first or the last element of the sequence. Each event (tone, word) had a duration of 500ms and the four events in the sequence were presented with a silent inter-stimulus interval of 40ms. The software Presentation (Neurobehavioral systems) was used to run the experiment and record the responses.

For the musical task, six piano tones were used (C3, D3, E3, F3, G3, and A3, Cubase 5.1 software, i.e., with F0 ranging from 262 to 440Hz). For the different trials, all the changes between S1 and S2 entailed a change of melodic contour (i.e., a change in the pattern of up

and downs created by the intervals). The changed tone in S2 created a pitch change between three and nine semi-tones from S1 and S2. For the verbal task, we used six monosyllabic French words differing only by their initial consonant, and all with the same fundamental frequency: "toux" (/tu/, cough), "bout" (/bu/, end), "loup" (/lu/, wolf), "goût" (/gu/, taste), "mou" (/mu/, flabby), "pou" (/pu/, head louse), spoken by a female voice, semi-synthesized (i.e., natural recordings were edited to equate loudness and F0 –at 230 Hz– across stimuli, see (32), for details). For different trials, we excluded changes of words between S1 and S2 corresponding to minimal phonetic pairs (i.e., changes included at least two phonetics differences), to decrease the difficulty of the verbal task.

In addition, we tested visual STM, to detect general STM disorders, which are not specific to auditory memory. A shape was presented to the participant on a computer screen. This shape was continuously distorted and returned to the initial shape (S1) in 2100 ms (i.e., the duration of the auditory sequences), followed by a blank screen of 1sec, and then the same shape was distorted again (S2), either exactly in the same way or differently (different related to the intensity and speed of the deformation). The shapes were designed with Bezier curves to minimize possible simple verbal labels to remember the shape or its deformation (40).

There was one block for each material type (words, tones, visual). At the beginning of each block, six example trials were presented. Then, for each material type, 32 trials were presented (16 same and 16 different pairs). For each trial, the participant had to choose if the two sequences were the same or different. They had two seconds to provide their answer after the end of S2 and they indicated their answer by a button press (for one 85-year-old patient who had never used a computer the experimenter recorded the answers by button press). The order of the two auditory tasks was counter-balanced across participants, and the visual condition was always presented at the end (Fig. 1). For each material, the trials in each block were presented in a different pseudorandom order for each participant, with the constraint that the same type of trial (same or different) could not be repeated more than three times in a row.

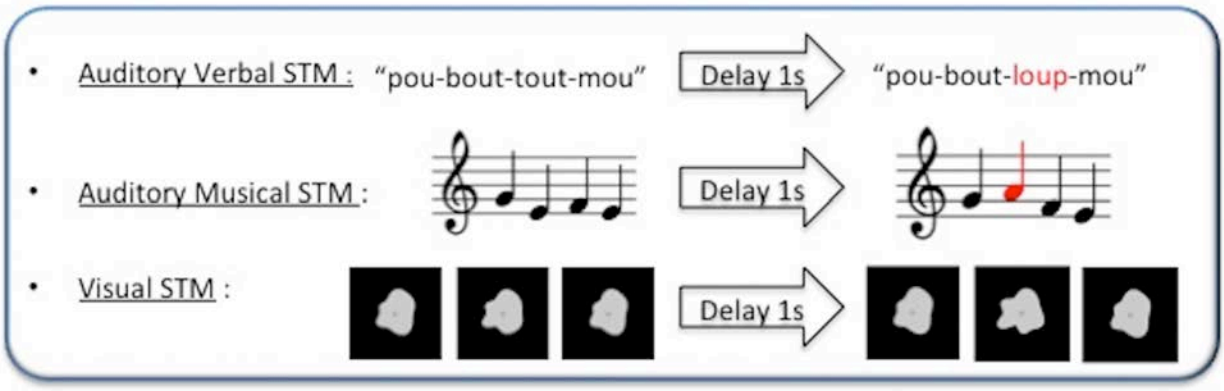

Figure 1: Neuropsychological assessment for STM.

For each task, participant have to indicate if the two sequences are the same or different. All sequences have the same duration (2.1 s).

4. Statistical analyses for the behavioral data

For the demographical and the neuropsychological data, we first compared patients and controls and then compared patients with left lesions to patients with right lesions with t-tests. Chi2 tests were used to compare sex ratios.

For the STM tasks, we computed *d'* and *c*, according to signal detection theory (41), for each material type for each participant. *d'* corresponds to the sensitivity of the participant to perceive a difference between S1 and S2, and so to his/her performance at the task. The criterion c corresponds to the response bias. Positive values for c indicate a tendency to answer "same", negative values indicate a tendency to answer "different". The correction of d' and c measures used 1/number of same trials for cases without false alarms and 1-1/number of different trials for the maximum number of hits. *d'* and *c* were analyzed with (1) a 2x3 ANOVA with Group (patients vs. control participants) as the between-participants factor and Condition (words, tones, visual) as the within-participant factor, and (2) a 2x3 ANOVA with Patient group (patients with left lesions vs. patients with right lesions) as the between-participants factor and Condition (words, tones, visual) as the within-participant factor. Post-hoc analyses for significant effects or interactions were carried out using Fisher LSD tests.

We also used multiple regression models to correlate performance on STM tasks with the results of neuropsychological assessment. As we could not collect Pitch Discrimination Threshold data for two patients (P007 and P019), the regression analyses were carried out with 18 patients.

5. Lesion Analysis

For 19 out of the 20 patients, an anatomical MRI was acquired at the end of the second session of behavioral tests. One patient had cardiac surgery with placement of an implantable defibrillator before the second appointment. The analysis of his lesion was thus conducted on a T2Flair MRI performed 12 months after stroke.

Participant lesions were imaged with 3D MRI scans (Magnetom Prisma Siemens 3T MRI equipped with a 64-channel head/neck coil), with T1, T2 and T2FLAIR sequences (Fluid-Attenuated Inversion Recovery scan: TR=5000ms, TE=349ms, TI=1008ms, FOV=224x224mm, sagittal acquisition, slice thickness = 0.9mm, 192 slices). Lesions were drawn manually by a trained neurologist[†] on the individual's T2FLAIR MRI images in native space, using MITK 3M3 (Mint Medical Ins, USA) and then checked against the T1 and T2 images. MRI images and lesions masks were normalized into the MNI (Montreal Neurological Institute) space, using the standard linear spatial normalization procedure from SPM12 (Functional Imaging Laboratory, London, UK) in Matlab R2014B (Mathworks Inc., Natick, MA, USA).

To get insights into the anatomic correlates of the auditory STM tasks, we used "Voxel-based Lesion Symptom Mapping" (VLSM, (42), with the toolbox "VLSM2" in Matlab R2014B (Mathworks Inc., Natick, MA, USA)). In VLSM, a t-test is used at each voxel to compare performance on a given measure (e.g., musical STM performance) in individuals with a lesion at that voxel versus individuals without a lesion at that voxel (based on the lesion masks created during the previous step). The advantage of the VLSM approach, compared to a ROI-based approach is that it does not make any a priori assumptions regarding relevant subgroups of patients (e.g. patients with temporal lesions vs. patients with frontal or parietal ones, see Supplementary Fig. 1 for such an analysis). As the present study included only 20 patients[‡] which is below the current practice in the VLSM literature, with typically more than 40 patients tested (44), the present analysis was exploratory and used a liberal statistical threshold cut-off with alpha set at 0.001 at each voxel. To increase the power of the VLSM analysis we combined the data from both hemispheres by flipping the right lesions on the left hemisphere (see below). The VLSM analysis was run for the *d'* for the three STM tasks separately.

[†] Manual drawing of lesions was also performed by a second rater. We then re-ran the VLSM analysis with this second set of lesion masks, which led to results in agreement with those reported here.

[‡] Note however that the current study is one of the largest lesion-led studies in terms of number of stroke patients included in the music cognition domain (with 20 patients as in (5,43)). To the best of our knowledge, only the studies by Särkämo et al. (2009, 2010) were larger in terms of sample size (n=53).

C. Results

1. Participants

Demographic data are presented in Tables 1 and 2. Twenty patients and fourteen control participants were included. Among the 20 patients, ten had lesions in the left hemisphere and ten in the right hemisphere. The delays since stroke varied from 4 to 52 months, for a median of 13 months. The volumes of the residual lesions at distance from the stroke varied from 0.1 to 68.4mL, for a median of 9.45mL. There were no significant differences between patients with left and right lesions for the delay since stroke and lesions size.

The three groups were comparable for sex ratio, level of education, music education, and audiometry. All participants were right-handed (right writing hand).

	Right lesions (N = 10)	Left lesions (N = 10)	Control participants (N = 14)	p (group effect) Patients (N=20) vs. Control participants (N=14)	p (group effect) Left (N=10) vs. Right (N=10) lesions
Sex ratio M/F	4/6	7/3	7/7	p = 0.8	p = 0.2
Age (years)	58.8 ± 10.3 (48-74)	62.3 ± 13.2 (37-85)	59.1 ± 10.7 (37-73)	p = 0.7	p = 0.5
Education (years)	10.8 ± 2.9 (5-14)	12.2 ± 4.1 (5-16)	13.4 ± 4 (5-20)	p = 0.2	p = 0.4
Musical education (years)	0.3 ± 0.9 (0-3)	5.9 ± 15.8 (0-50)	3.7 ± 11.9 (0-45)	p = 0.9	p = 0.3
Time since stroke (months)	18 ± 18 (4-52)	16.6 ± 13.3 (7-50)	NA	NA	p = 0.8
Size of lesion (mL)	16.1 ± 19.7 (0.1-67.6)	21.6 ± 20.1 (1-68.4)	NA	NA	p = 0.5
RE Audiometry (dB)	18.9 ± 12.2 (7.5-46.25)	22.6 ± 8.5 (8.75-36.25)	19.9 ± 9.6 (7.5-42.5)	p = 0.8	p = 0.4
LE Audiometry (dB)	21.1 ± 13.9 (6.25-46.25)	21.5 ± 12.4 (7.5-43.75)	17.4 ± 11.6 (0-42.5)	p = 0.4	p = 0.9

Table 1: Demographic data of patients and control participants: *for each parameter the group average, standard deviation and range is reported.*

The audiometry is calculated as the average hearing threshold at 500, 1000, 2000 and 4000Hz for each ear. RE: right ear; LE: left ear

Patient	Sex	Age (years)	Education (years)	Musical education (years)	Time since stroke (months)	Laterality of lesion	Size of Lesion (ml)	RE Audio-metry (dB)	LE Audio-metry (dB)
P001	F	69	5	0	10	R	9.4	16.25	8.75
P002	F	62	12	0	10	R	19	16.25	20
P005	F	60	12	0	4	R	0.1	46.25	45
P008	F	49	12	0	52	R	7	22.5	13.75
P009	M	53	11	0	14	R	3.7	11.25	20
P012	M	48	14	3	5	R	4.7	7.5	6.25
P013	M	51	12	0	14	R	26.4	13.75	22.5
P016	F	49	12	0	13	R	9.5	10	15
P019	F	74	6	0	51	R	67.6	33.75	46.25
P020	M	73	12	0	7	R	13.8	11.25	13.75
P003	M	66	14	0	7	L	24.5	23.75	15
P004	M	56	12	0	9	L	7.8	8.75	7.5
P006	M	65	5	50	20	L	8.8	18.75	17.5
P007	M	50	16	0	26	L	68.4	25	26.25
P010	M	56	11	0	13	L	28	17.5	10
P011	M	72	14	0	17	L	11.2	36.25	43.75
P014	F	85	5	0	7	L	6.1	32.5	33.75
P015	M	70	16	0	9	L	38.4	30	33.75
P017	F	66	14	0	8	L	21.7	15	18.75
P018	F	37	15	9	50	L	1	18.75	8.75

Table 2: Demographic data of patients

R: right; L: left. See Table 1 for details.

2. Neuropsychological assessment

The results of neuropsychological assessment are presented in Table 3. Patients had lower MMSE scores than control participants. But with the MMSE cut-off score adapted for age and education, only two patients (P003 and P004) had a mild cognitive disorder. Patients had reduced fluencies (lexical and categorical) when compared to control participants. There were no differences between the two groups of patients for the neuropsychological assessment. All participants obtained the maximal score for the battery of denomination, BARD (10/10).

MBEA

The cut-offs (mean -2SD) were calculated from MBEA scores of 421 participants (http://www.brams.umontreal.ca/plab/publications/article/57#extras) (39). The cut-off score

to be considered as amusic is ≤ 22.4/30 for participants under sixty years, and ≤ 21.6/30 for participants over sixty years.

Based on these criterions, three patients and two control participants were diagnosed as amusics. The three patients (P003, P014 and P015) had lesions in the left hemisphere and their scores were 18.5/30, 17.7/30 and 18.7/30, respectively. They were all older than sixty. The two control participants (congenital amusics) had MBEA scores of 20.5/30 and 20.7/30 and they were both under sixty years old.

At the group level, there was no difference between the patients and control participants for the MBEA score ($F(1,32)=0.7$; $p=0.4$) and between the two groups of patients (left vs. right lesion) ($F(1,18)=2.1$; $p=0.2$).

PDT

The pitch discrimination thresholds were ranging from 0.15 to 4.67 semi-tones in patients and from 0.17 to 4.42 semi-tones in control participants (see Table 3). PDT inferior to one semi-tone is considered normal in young people, but a decrease of frequency selectivity was expected with aging (45). There was no significant difference between patients and control participants ($F(1,30)=1$; $p=0.3$) and between the two groups of patients ($F(1,16)=0.02$; $p=0.9$).

	Right lesions (N = 10)	Left lesions (N = 10)	Control participants (N = 14)	p (group effect) Patients (N=20) vs. Control participants (N=14)	p (group effect) Left (N=10) vs. Right (N=10) lesions
MMSE (/30)	**27.8 ± 1.8 (25-30)**	**27.3 ± 3.1 (23-30)**	29.2 ± 0.9 (27-30)	**p = 0.02**	p = 0.7
BARD (/10)	10 ± 0	10 ± 0	10 ± 0	NA	NA
Lexical fluencies	**17.1 ± 7.7 (3-25)**	**16.3 ± 8 (6-28)**	22.7 ± 7.1 (13-35)	**p = 0.03**	p = 0.8
Categorical fluencies	**25 ± 6.1 (15-36)**	**26.5 ± 8 (15-35)**	31.9 ± 9.9 (18-53)	**p = 0.04**	p = 0.6
PDT (semi-tones)	1.4 ± 1 (0.15-3.27)	1.5 ± 1.6 (0.16-4.67)	1 ± 1.2 (0.17-4.42)	p = 0.3	p = 0.9
MBEA score (/30)	24.6 ± 1.8 (22.5-27.5)	22.8 ± 3.5 (17.67-26.67)	24.5 ± 2.3 (20.5-27.83)	p = 0.4	p = 0.2

Table 3: Neuropsychological assessment for all participants (mean, SD and range for the different parameters tested).

Patients had a lower MMSE score in comparison with control participants (but note that all except two were normal in comparison to age and education-related norm). They also had reduced fluencies (lexical and categorical) in comparison with control participants (scores highlighted in bold).

3. Short-term memory tasks

For performance in *d'* (Figure 2), the first ANOVA comparing patients and controls revealed a significant main effect of condition ($F(2,64)=7.6$; $p=0.001$): post-hoc analyses showed that *d'* of the auditory musical task (tones) was higher than *d'* of the auditory verbal task ($p=0.001$) and the visual task ($p<0.001$), while *d'* of verbal and visual tasks did not differ ($p=0.87$). There was a significant main effect of group ($F(1,32)=6.2$; $p=0.02$), with patients having lower performance than control participants. The interaction between the two factors was not significant ($F(2,64)=0.005$; $p=0.99$). The second ANOVA comparing the two patient groups confirmed the main effect of condition ($F(2,36)=3.73$; $p=0.03$), and showed that there was no difference between the two groups of patients ($F(1,18)=0.0003$; $p>0.98$), and no significant interaction between the factors Group and Condition ($F(2,36)=0.35$; $p=0.7$).

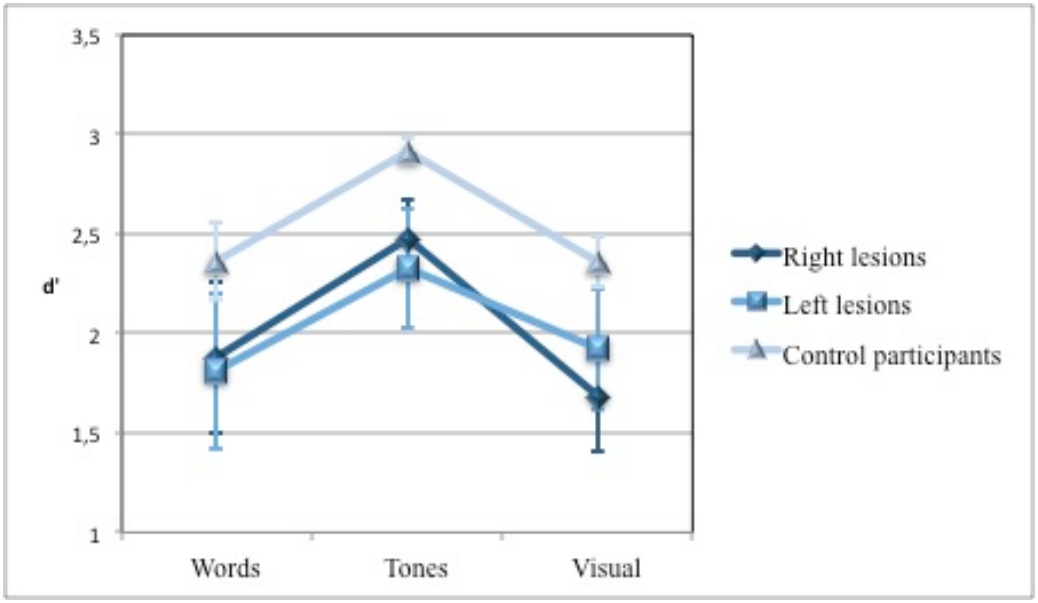

Figure 2: Performance (d') for short-term memory tasks presented as a function of material and participant group

d' for the three groups (patients with left lesions, patients with right lesions, control participants) for the three STM tasks (words, tones, visual). Overall the patients had lower

performances in comparison with control participants, regardless of the material to be memorized. The musical task was easier than the verbal and visual tasks for all groups.

The same analyses were performed for the criterion *c*. For the first analysis (patients vs. controls), only the main effect of group was significant: patients had a higher criterion c (c=0.21±0.32, mean±SD) in comparison with control participants (c=0.06±0.24) ($F(1,32)=4.7$; $p=0.04$). The main effect of condition and its interaction with group were not significant ($p>0.1$). For the second analysis (patients with left lesions vs. patients with right lesions), there was no significant effect (all $p>0.3$).

Overall, analyses of *d'* and the criterion *c* in STM tasks revealed that patients had lower performance than controls in all tasks and that this was due to missing differences between S1 and S2 (they answered "same" more often than did control participants). There was no significant difference between patients with left or right lesions as groups for any of the measures of interest.

The individual results (Table 4 and Supplementary Fig.1) revealed that five patients had deficits in auditory verbal STM (with a cut-off defined as 2SD below the mean of the control participants): three patients with a lesion in the right hemisphere and two patients with a lesion in the left hemisphere; nine patients had deficits in auditory musical STM: four with a right-hemisphere lesion and five with a left-hemisphere lesion; and six patients had deficits in visual STM: three with a left-hemisphere lesion and three with a right-hemisphere lesion.

Among the five patients with deficits in verbal STM, four had also deficits in musical STM, and three of the five also in visual STM. Two of these cases are noteworthy: P009 had verbal, but not musical auditory STM deficits, and P003 had the second largest deficit in verbal STM of patients in the present sample, but he only had a small impairment for musical STM. In contrast, among the nine patients with deficits in musical STM, four did not have any deficit in verbal and visual STM (we describe the most striking case, P014, below) and one had deficits in musical and visual STM, but not verbal STM. Finally three patients had only a visual STM deficit.

Patients	Lesion	d' words	d' tones	d' visual
P001	R	**0.887**	**1.308**	1.853
P002	R	2.376	**2.023**	2.023
P005	R	2.326	2.685	2.257
P008	R	3.069	**2.209**	2.209
P009	R	1.163	3.069	**1.11**
P012	R	2.602	3.069	3
P013	R	2.685	3.069	**0.993**
P016	R	3.036	2.422	2.038
P019	R	**-0.821**	**1.809**	**-0.294**
P020	R	1.469	3.069	1.692
P003	L	**-0.646**	**2.209**	1.438
P004	L	1.853	3.069	1.639
P006	L	1.825	3.069	**1.349**
P007	L	1.562	2.685	3.069
P010	L	3.069	3.069	3.069
P011	L	**0.25**	**1.659**	**1.163**
P014	L	2.422	**0.075**	1.534
P015	L	1.639	**1.965**	**0.318**
P017	L	3.069	3.069	3.036
P018	L	3.069	**2.376**	2.612
Cut-off		0.9	2.4	1.4
Cut-off without outlier		1.4	NA	NA

Table 4: Individual performance of the patients for the STM tasks

The cut-offs are defined as below 2SD from the mean of control participants' performance. Performance below the cut-off are highlighted in bold and with a grey background. For the verbal STM task, one control participant was below the cut-off (d'=0.588), so we recalculated the cut-off without this data point (last line of the table). Performances below this corrected cut-off are highlighted with a grey background.

L=left; R=right

Additionally, we tested the correlations between the performances (*d'*) in the different STM tasks. For patients, *d'* for the verbal task was correlated with *d'* for the visual task ($r(18)=0.64$; $p=0.003$), but not with the musical task ($r(18)=0.26$; $p=0.3$), and the *d'* of the musical and visual tasks did not correlate ($r(18)=0.32$; $p=0.2$). For control participants, there was no correlation between the three tasks ($p>0.17$).

Finally, as some of the participants had elevated PDT, we checked whether these pitch discrimination deficits might hinder the performance in the musical STM task and cause the observed between-group differences. For that purpose, the different trials in the musical STM

task were sorted into two classes, corresponding to large changes between S1 and S2 (at least 5 semi-tones) and small changes (3 or 4 semi-tone changes). Each of the two classes contained 8 trials (per participant). Note that the large changes were above the PDT of every participant. d' were recalculated for each class of trials and participant, and analyzed with an ANOVA with Group (Patients vs. Controls) and Size of change as factors. The ANOVA revealed a main effect of Group ($F(1,32)=4.502$; $p=0.04$) with controls outperforming patients (as expected from the main analysis), and a main effect of Size of change ($F(1,32)=8,016$; $p=0.008$) as expected (see also (34)). However, the critical Group-by-Size of change interaction was not significant ($F(1,32)=0.511$; $p=0.5$). The patients' musical STM deficit was thus observed for all sizes of changes, including changes larger than the worst PDT observed.

4. Case report of a selective deficit to music

We here discuss the case of P014, an 85-year-old woman without any musical training. She had a stroke in the left hemisphere (resulting in two lesions in frontal and parietal areas) seven months before the present study. The MBEA scores revealed her as amusic: her mean MBEA score was 17.7/30 (cut-off = 21.6/30), with a score at chance level (15/30) for each of the first three sub-tests. In addition, she had an elevated pitch discrimination threshold at 3.3 semi-tones. Her performance for the musical STM task (d'=0.075) was 9 SD below the cut-off, while her performance for verbal and visual STM tasks was normal (d'=2.42 and d'=1.53 respectively). In sum, the results reveal that she performed at chance level for all musical tasks involving pitch memory (the first three sub-tests of the MBEA, the musical STM task investigated here) and that her deficit was specific to music. Interestingly, the patient had no complaints about potential difficulties with music perception.

5. Regression models between the neuropsychological assessments and performance in the STM tasks

Multiple regression models were performed aiming to explain performance on each STM task by the results of neuropsychological assessments for all participants. For the d' of each task, we aimed to explain performance with age, MBEA score, PDT, MMSE score, lexical and categorical fluencies.

For the verbal task, the regression model was marginally significant ($F(6,25)=2.2$; $r^2=0.34$; $p=0.08$), with lexical fluency as the only significant predictor ($\beta=0.06$; $p=0.04$). For the musical task, the model was significant ($F(6,25)=4.2$; $r^2=0.50$; $p=0.005$), with PDT as the only (marginally) significant predictor of performance ($\beta=-0.20$; $p=0.07$). For the visual task, the model was not significant ($F(6,25)=1.7$; $r^2=0.29$; $p=0.16$). The corresponding scatter plots between the performance of the STM tasks and the neuropsychological assessment are shown in Figure 3.

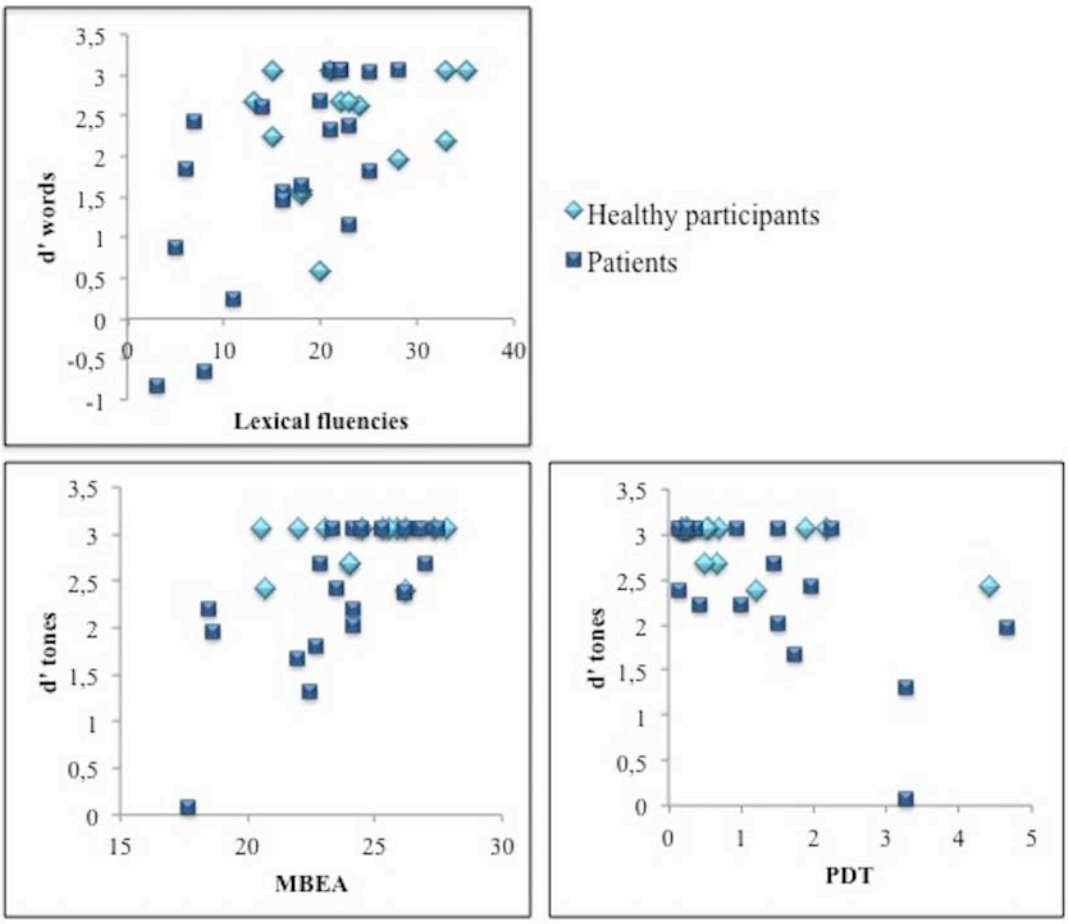

Figure 3: Scatter plots: Performance (d') in STM tasks as a function of the neuropsychological assessment for all participants.

There is a significant relation between the performance for the verbal STM task and the lexical fluencies across all participants (see main text for the results of the regression analysis). There is a significant relation between the performance for the musical STM task and the MBEA in patients and a significant relation between this STM task and the PDT in controls and across all participants. Lexical fluencies are expressed as the number of words produced in two minutes. For the MBEA, the maximum score is 30/30, chance level is 15/30. PDT is measured in semitones.

In a second step, we performed these regression analyses separately for each group of participants. For control participants, the model was not significant for the verbal task ($F(6,7)=0.7$; $r^2=0.38$; $p=0.6$) and the visual task ($F(6,7)=2.7$; $r^2=0.69$; $p=0.1$), but it was significant for the musical task ($F(6,7)=4.2$; $r^2=0.78$; $p=0.04$), with PDT ($\beta=-0.25$; $p=0.005$) and lexical fluency ($\beta=0.03$; $p=0.02$) as significant predictors. For patients, we added the size of the lesions as an explanatory factor. Note that none of the performance measure from the neuropsychological tasks and STM tasks was correlated with the size of the lesions ($p>0.10$). The model was not significant for the verbal task ($F(7,10)=1.8$; $r^2=0.56$; $p=0.19$) and the visual task ($F(7,10)=1.1$; $r^2=0.44$; $p=0.43$), but it was significant for the musical task ($F(7,10)=4.2$; $r^2=0.75$; $p=0.02$), with only the MBEA score being a significant predictor of performance ($\beta=0.20$; $p=0.03$).

6. Lesion analysis

The location of all patients' lesions is shown in Table 5 and illustrated on individual T2Flair MRIs in Figure 4. For each of the STM tasks, we performed VLSM analyses. As performance for the STM tasks did not differ depending on the lateralization of the lesion, we combined the data from both hemispheres by flipping the right lesions on the left hemisphere aiming to increase the power of the statistical analysis. The overlay of the lesions for the 20 patients showed a maximum overlap of nine lesions in the same voxel (Fig. 5).

		Temporal				Insula			Frontal		Parietal		BG
		HG med.	HG lat.	STG (excl. HG)	MTG	Post.	Med	Ant.	Pre-cent.	IFG	Post-cent	SMG	
P001	R					X	X						X
P002	R	X		X		X					X	X	
P005	R					X							
P008	R							X	X	X			
P009	R						X		X				
P012	R		X	X									
P013	R				X						X		
P016	R					X						X	
P019	R					X			X		X	X	
P020	R						X	X	X	X	X		
P003	L					X					X		
P004	L					X						X	
P006	L								X				
P007	L					X					X	X	
P010	L						X	X	X	X			
P011	L					X			X				
P014	L						X		X	X	X		
P015	L							X		X			
P017	L			X									
P018	L									X			

<u>Table 5:</u> Location of the lesions of the 20 patients.

Abbreviations: L=left lesion; R=right lesion; BG=basal ganglia; SMG=supra-marginal gyrus; IFG=inferior frontal gyrus; STG=Superior temporal gyrus; MTG=medium temporal gyrus; HG=Heschl gyrus; med=medial; lat=lateral; excl=excluding; post=posterior; ant=anterior; cent=central

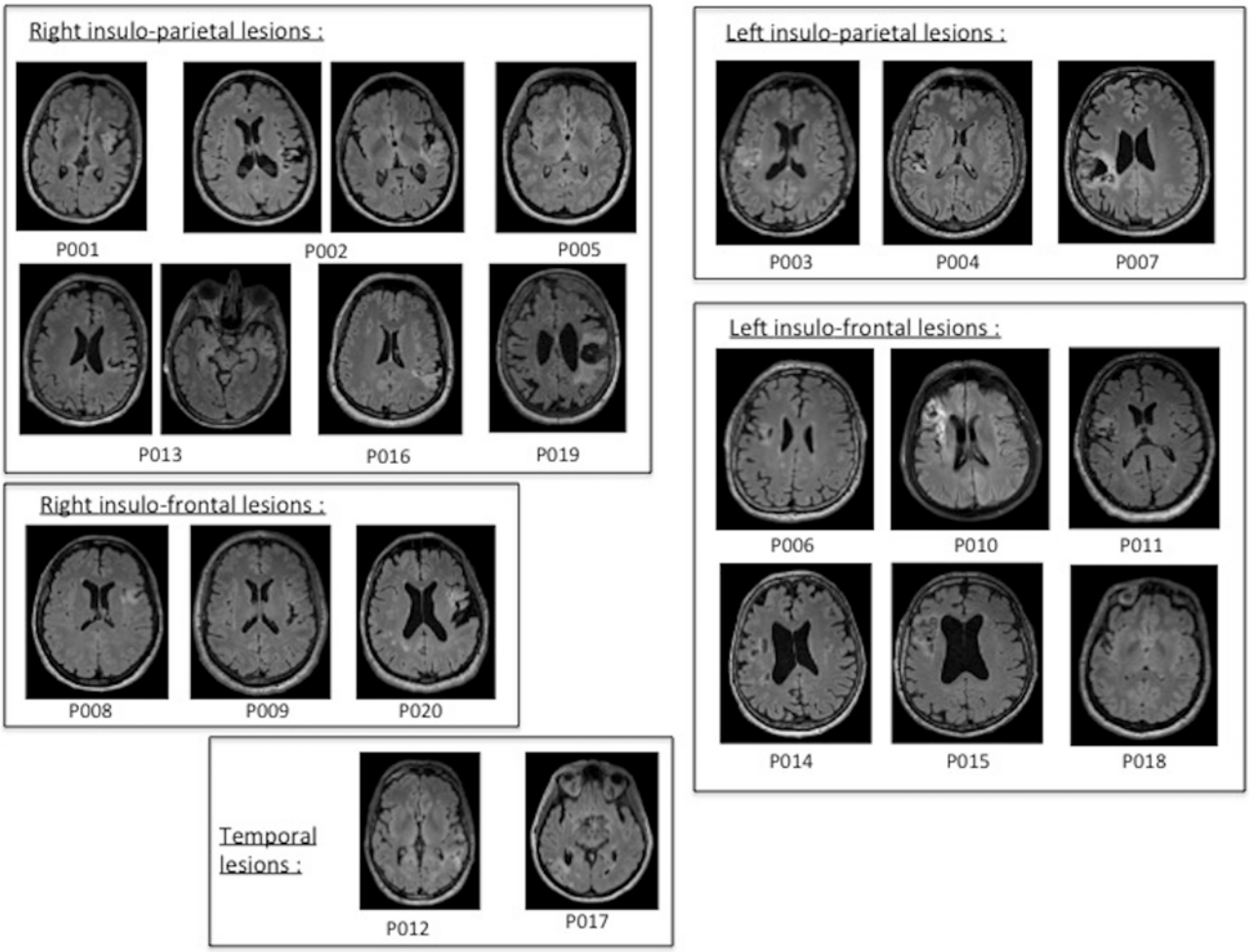

Figure 4: MRI of the 20 patients

Axial slices, T2Flair sequences, showing the focal brain lesions.

The significant clusters resulting from the VLSM analyses are presented in Table 6 and Figure 6. They were grouped mainly in the central region, parietal lobe, and insula. Lesions in inferior fronto-parietal operculum (rolandic operculum, inferior pre-central and post-central gyrus) were associated with deficits in all three STM tasks. Lesions in the insula were associated to lower performance in the musical task, and parietal lesions with lower performance in the verbal task.

	Cluster Volume	px	py	pz	cx	cy	cz	Max T	Location
Words	4854	±59	-12	11	±51	-18	31	5.93	Fronto-parietal operculum
	11	±44	0	21	±42	0	21	4.46	Fronto-parietal operculum
	227	±41	-17	40	±46	-18	47	3.68	Post-central gyrus
Tones	14	±32	-5	13	±33	-5	14	5	Insula
	93	±39	-2	-6	±41	-3	-4	4.63	Insula
	18	±54	-5	23	±54	-6	22	4.14	Fronto-parietal operculum
Visual	242	±33	-8	20	±40	-8	20	4.42	Fronto-parietal operculum
	12	±41	-1	21	±43	0	21	4.19	Fronto-parietal operculum
	20	±59	-2	21	±57	-3	21	3.84	Fronto-parietal operculum

Table 6: Significant clusters for the STM tasks in VLSM analysis.

The volume of clusters is in mm^3. The MNI coordinates of the peak of clusters (px, py, pz) and the MNI coordinates of the center of clusters (cx, cy, cz) are represented. These clusters indicate that a lesion at this location had an effect on STM tasks ($p<0.001$).

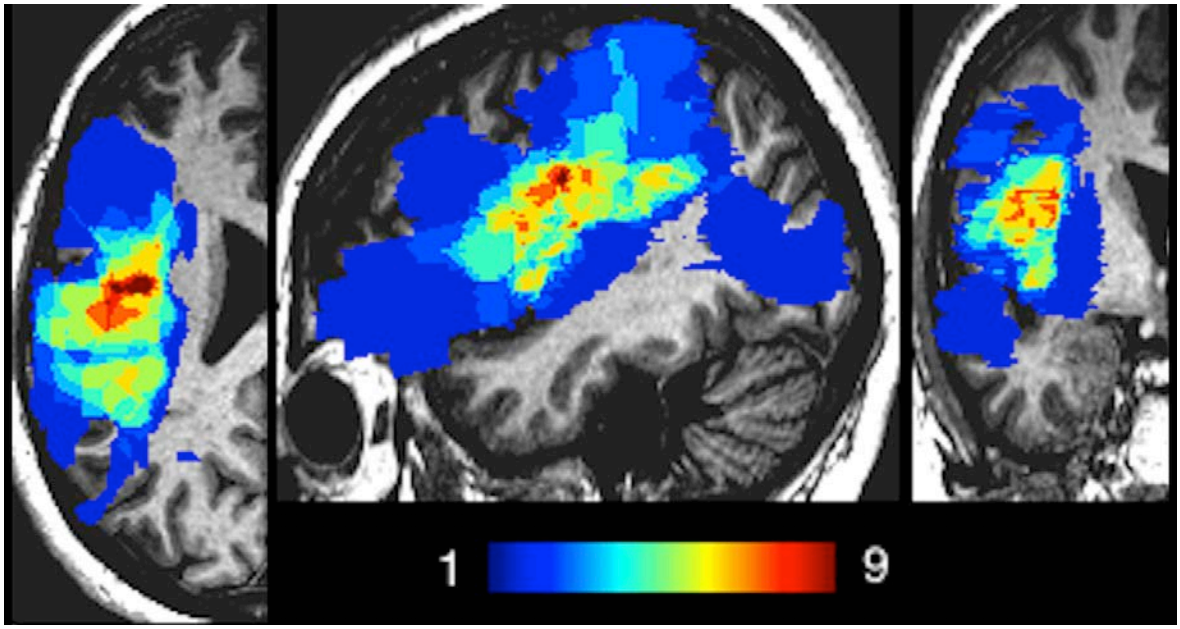

Figure 5: Overlay of the 20 lesions

The number of patients having a lesion at each voxel is color-coded. The ten lesions in the right hemisphere have been flipped on left hemisphere for the VLSM analysis. There is a maximum of nine patients having a lesion in the same voxel.

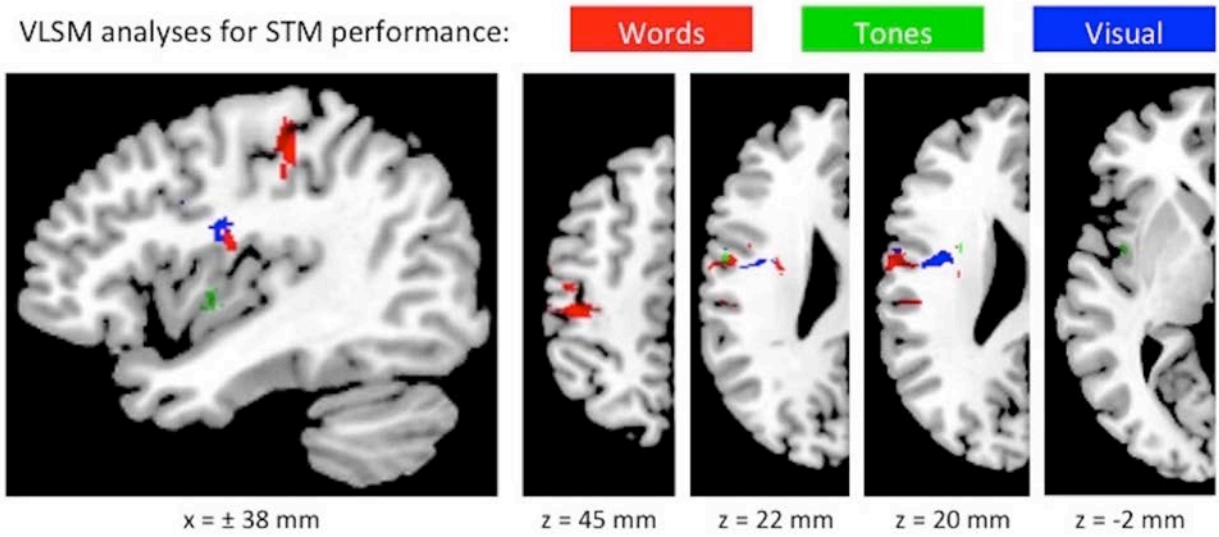

Figure 6: Results of the VLSM analysis.

For d' in each STM task (words, tones, visual), a VLSM analysis was run on the lesion masks of the twenty patients. Significant clusters ($p<0.001$, see Table 6 for peak and center coordinates) are depicted with a color for each task (red for words, green for notes and blue for visual). The VLSM analysis highlighted the involvement of dorsal areas for all STM tasks, particularly the words and visual tasks, and of more ventral areas for the musical task. Clusters are superimposed on the MNI template, and MNI coordinates are specified for each slice.

D. Discussion

The present study investigated deficits of verbal and musical auditory STM after stroke, and the cerebral correlates of the observed behavioral deficits using a voxel-based lesion symptom mapping approach. We used STM tasks that were well matched across materials, and we performed a thorough neuropsychological assessment covering peripheral auditory processing, language and music perception. We included patients with focal cortical lesions in regions of interest for auditory STM, i.e., temporo-parieto-frontal areas in the territory of the middle cerebral artery, based on previous findings of neuropsychological and neuroimaging studies. None of the patients had severe aphasia, neither severe functional or cognitive disability.

The two groups of patients (with either right- or left-hemisphere lesions) were matched for demographic data and also with control participants. For neuropsychological assessment and performance in the STM tasks, patients with a right- or a left-sided lesion did

not differ. In comparison to the control participants, patients had lower scores on MMSE and verbal fluencies. This result suggests that stroke affected patients' general cognition, including language. STM deficits might contribute to these general cognitive difficulties. However, note that even though they had lower scores than the controls tested here, all patients (except two) were normal on the MMSE when considering age and education-related norms. For the STM tasks, patients had lower performances in comparison with control participants, regardless of the material type (words, tones, visual). The individual data revealed a double dissociation between some patients exhibiting verbal deficits without musical deficits or the reverse. The VLSM analysis showed the importance of inferior fronto-parietal operculum for auditory and visual STM. However, the sample size did not allow us to separate the two hemispheres in the VLSM analysis, and thus although the two patient groups did not differ as a whole, we cannot exclude differences between the two hemispheres regarding the involvement of specific brain structures in auditory and visual STM.

In the following, we discuss the selectivity of STM deficits, in particular with respect to the side of the lesion, the clinical application of our new assessment tool, and the brain correlates of STM as observed with VLSM, and finally, we propose an interpretation of the data within a connectionist framework.

1. Short-term memory deficits after stroke

We have studied auditory STM in brain-damaged patients, by comparing performance in the same task-setup applied to tones and to words. We also have studied visual STM, to evidence potential STM disorders, which were not specific for the auditory modality. The results showed that the musical task was easier than the verbal and visual tasks, which were similar in difficulty. Overall, stroke patients had poorer performance in all STM tasks, in comparison with control participants, regardless of the condition (words, tones, visual). Based on prior neuroimaging studies, we had targeted lesions of the temporal, parietal and frontal lobes.

In contrast to our hypothesis expecting more verbal deficits with left-hemisphere lesions and more musical deficits with right-hemisphere lesions, performance in the STM tasks (for words, tones and visual materials) did not differ between patients having lesions in either right or left hemispheres. Also, there were as many patients with STM deficits with lesions in either hemisphere. Overall, the present data suggest that bilateral networks are involved in verbal, tone, and visual memory.

For musical STM, previous imaging studies had shown the bilateral involvement of brain structures: using positron emission tomography (PET), Zatorre et al. showed that for short-term pitch retention in control participants, the right fronto-temporal cortex was activated (30). Using magneto-encephalography, Albouy et al. showed that bilateral fronto-temporal areas are involved in STM for pitch sequences (34). Other PET and fMRI studies congruently showed the implication of both hemispheres in auditory musical STM (25,46).

For verbal STM, most neuroimaging studies showed predominant activation of the left hemisphere (21), but bilateral activation has also been shown, notably in the insula (23), the temporal regions (47) and the parietal regions (48). However, the overall left-hemisphere bias observed in verbal working memory tasks should be taken with caution as most imaging studies use visually-presented verbal stimuli, whereas the activation is more bilateral in inferior parietal areas when auditory verbal stimuli are used (49,50), as in our study. Furthermore, the verbal STM task used here mostly requires phonological memory with almost no demands on semantic processes and no demands on syntactic processes. Unlike semantic processing which involves the left inferior frontal gyrus, phonological processing does not necessarily recruit frontal areas and is associated to the activation of both hemispheres for fronto-temporal regions (47,51). For visual STM, also both hemispheres have been shown to be implicated (52).

The individual results showed double dissociations between patients exhibiting verbal deficits without musical deficits and the reverse (see Table 4 and supplemental Figure). Also, there was no correlation between performance in the musical STM task and the verbal STM task in the patient group. One main conclusion, which can thus be drawn from the observed data, is that the cerebral networks involved in musical and verbal STM are to some extent distinct, and that the distinction between networks is not the laterality (relative involvement of both hemispheres).

2. Clinical application: interest of testing auditory short-term memory after stroke

Until now, classical neuropsychological assessments testing auditory STM use mostly verbal material, and for the testing of music processing, the MBEA is used. We propose a new STM test, which has the advantage to apply the same paradigm setup to different materials: it uses verbal, musical and visual material and is short (about twenty minutes), what is important to test brain-damaged patients, to limit fatigue and lack of concentration. As

discussed above, the tests also allow for observing selective deficits for the different materials (53).

The multiple regression models showed that performance in the verbal task was correlated with the lexical fluencies for all participants. This is in agreement with previously reported close links between auditory verbal STM and language production (54–56). For example, Potagas et al. showed a strong correlation between aphasia scores and verbal STM performance in aphasic patients.

Performance in the musical STM was correlated with the PDT for all participants and with the MBEA for all patients. Considering the paradigm and material manipulation, we can make the hypothesis that both STM and pitch discrimination play a role for good performance in the musical STM. For the control participants, performance was related to their pitch discrimination threshold. However, for the patients, the STM performance was related to the MBEA score. As four of the six subtests of the MBEA engage auditory STM, in addition to pitch, interval, contour and rhythm discrimination, memory seems to be a critical factor for the patients. The musical short-term memory task involved changes of pitch between three and nine semi-tones. Three patients and one control participant had a higher PDT than three semi-tones (P001, P014, P015, C009). However as the musical STM deficit of the patient was observed for both small and large changes (above all participants' PDT) between the two tone sequences, this deficit could not be solely explained by the increased PDT of some patients.

Following the diagnosis criteria of the MBEA, three patients and two control participants emerged as amusic, even though none had specific complaints about music. The three patients had lesions in the left hemisphere, but it is important to also consider that the two groups of patients (left vs. right lesion site) did not differ on the MBEA score. This observation is in agreement with previous report showing acquired amusia in brain-damaged patients with lesion in either hemisphere (3,5,57). The three amusic patients also had an auditory musical STM deficit. We reported the case of P014, which had a specific deficit on music with a MBEA score just above chance, an elevated PDT and a performance on musical STM task well under the cut-off.

The present study showed that different kinds of STM deficits could co-exist (musical, verbal, visual), even when the involved lesions are small and focal. In our study, even patients without cognitive deficit (assessed by MMSE and verbal fluencies) exhibited STM deficits. In a study investigating deficits of stroke patients, patients diagnosed as amusic also had other cognitive deficits, including working memory, semantic fluencies, executive functions and visuo-spatial cognition deficits, in comparison with the patients without acquired amusia (3,58). It therefore seems important to diagnose these associations of deficits, especially those

involving language and music, to provide appropriate reeducation. Our STM tasks could be used in neuropsychological assessment after stroke for this purpose.

3. Brain correlates of auditory short-term memory

Here, we studied the encoding and maintenance of information in STM, and did not require manipulation of information as in classical working memory tasks. With current tasks settings, participants didn't have time to repeat the sequences. We therefore expected that the parietal lobe would be more strongly involved in the verbal STM task than the frontal lobe, which is involved in the articulatory rehearsal component of working memory and speech production (15). In line with this hypothesis, the VLSM analysis revealed that lower performance in the verbal STM task was associated to lesions in the inferior fronto-parietal operculum and the post-central gyrus. These results are in agreement with previously reported neuroimaging data: The superior temporal gyrus is involved in speech perception and the parietal lobe is related to the phonological store (23,59).

The VLSM analysis further revealed that lower performance in the musical task was associated to lesions in the insula and the inferior fronto-parietal operculum (clusters in the operculum obtained by VLSM were very close for musical, verbal, and visual performance see Table 6 and Figure 6). For a task requiring the active retention of pitch, Zatorre et al. reported activations in inferior frontal and insular cortex, the planum temporale and the supramarginal gyrus (30). Stevens et al. have compared STM for tones, voice and words using fMRI (26). The tone condition produced clusters in posterior insula, in posterior inferior temporal gyrus and supramarginal gyrus. Our results converge with functional neuroimaging studies, showing the involvement of insula and fronto-parietal cortex in auditory musical STM.

Schulze et al. have reported a large overlap of neural resources underlying auditory STM for verbal and tonal information (Broca's area, premotor cortex, pre-SMA/SMA, left insular cortex and inferior parietal lobe) (60). Here, we observed an overlap in central areas (inferior fronto-parietal operculum), and the insula seems to be more strongly involved in musical STM and the parietal lobe more strongly involved in verbal STM. Overall, even if the results of the VLSM analysis should be taken with caution given the sample size, they are in keeping with prior findings in particular showing the importance of the parietal lobe for phonological short-term memory and the involvement of fronto-parietal regions in auditory STM in general. They further suggest an involvement of more ventral areas in musical STM,

an hypothesis that warrant further testing, but there already exist some indication from the neuroimaging literature in favor of this hypothesis.

Finally, the VLSM analysis revealed that lower performance in the visual task was associated to lesions in inferior fronto-parietal operculum (rolandic operculum, inferior pre-central and post-central gyrus). These regions were also involved in auditory STM in our data. We assume that these central regions are implicated in the integration of information in STM, be it visual or auditory. Potagas et al. showed that verbal and visual STM deficits can coexist in aphasic patients, and suggested that this is due to a possible primary deficit in information retention (56).

4. Auditory short-term memory and the dual stream model

In addition to the interpretation focusing on the impact of lesions in specific cortical areas on STM performance (see above), another possible explanation of the deficits is that the lesions are located on pathways connecting frontal and temporal lobes, which induces a disconnection that is responsible for the deficits.

The dual stream model of auditory processing refers to a dorsal pathway and a ventral pathway connecting auditory cortices and frontal areas. The dorsal pathway corresponds to the superior longitudinal fasciculus, including the arcuate fasciculus. The arcuate fasciculus connects frontal, parietal and temporal lobes. It is involved in language and visuo-spatial processing (61). The ventral pathway includes the extreme capsule fiber system and the inferior longitudinal fasciculus. Kellmeyer et al. suggest that the dorsal language pathway is a fast path for phonological memory and articulatory network from the left inferior parietal lobule to the left inferior frontal gyrus (62). The ventral language pathway is important for lexical and semantic processing. In singing, the dorsal pathway is involved in automatic, category-based sound analysis, while the ventral pathway is involved in conscious access to perceptual information (63). The importance of the dorsal pathway for music memory has already been emphasized (64). In keeping with this hypothesis, in congenital amusia, there is a disconnection of the right superior branch of arcuate fasciculus, in tractography (65,66), causing pitch perception and STM deficits.

In our study, lesions in the inferior fronto-parietal operculum were linked to STM deficits for both auditory and visual materials. The arcuate fasciculus goes through this area. As previous data have shown that the arcuate fasciculus is involved in phonological and

visuo-spatial processing, we make the hypothesis that lesions in the fronto-parietal operculum could cause a disconnection in the dorsal pathway, which might explain STM deficits. For the musical (pitch) task, our data suggest that both dorsal and ventral pathways are involved, in keeping with previous findings implicating both pathways in music processing (67). Indeed, the ventral pathway goes through the extreme capsule, right next to the insula. Future research should use the methodology of Diffusion Tensor Imaging to further shed light on the involvement of ventral and dorsal pathways in various types of STM, and in music processing in general.

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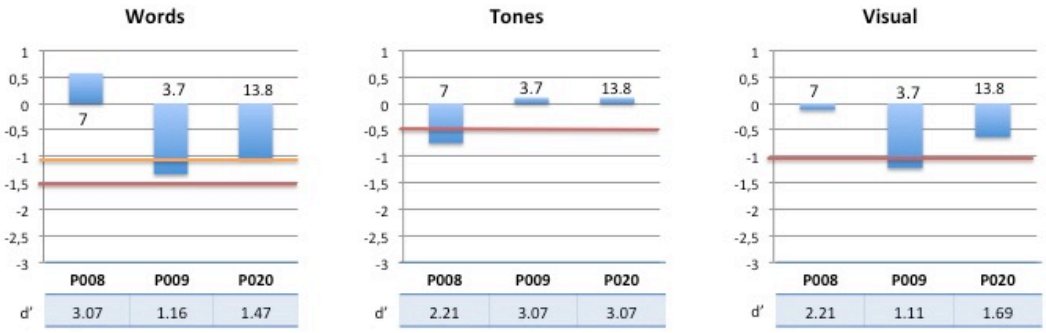
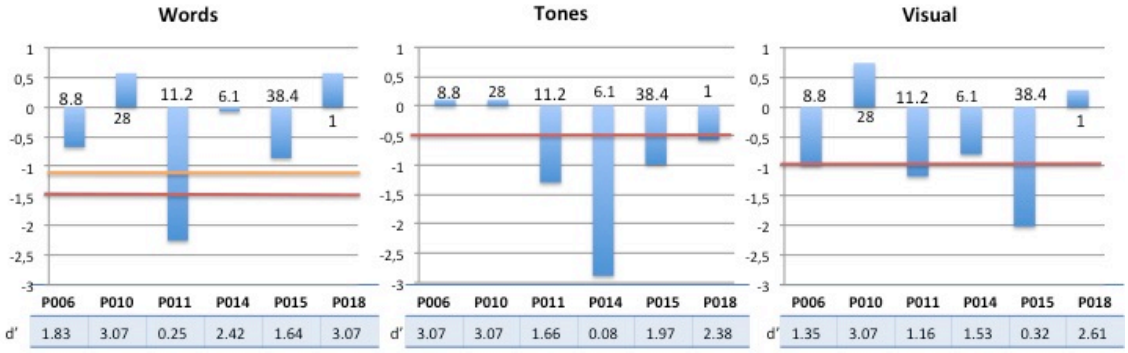
Right insulo-frontal lesions :



Left insulo-frontal lesions :



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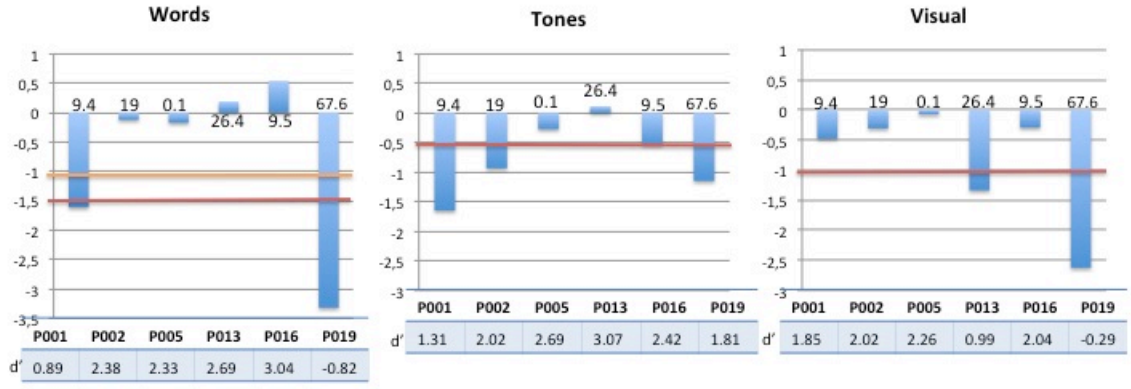

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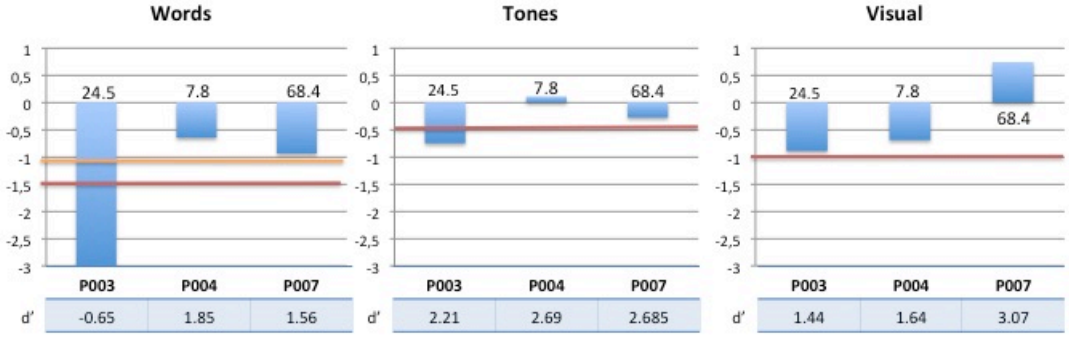

<u>Supplementary figure 1:</u> Individual results of patients for STM tasks

This figure presents the individual data of the patients with insulo-frontal or insulo-parietal lesions (in left or right hemispheres, see Figure 4 and Table 5 for details about the location of the lesions). The two patients with an isolated temporal lesion are not represented because they did not have any deficits on STM tasks (see P012 and P017 in Table 3). Note that amongst the patients with right insulo-parietal lesions, two had lesions extending into the temporal lobe (P002's lesion encompassed part of the STG and the medial part of HG, and P013's lesion encompassed part of the MTG). In abscissa is represented the patients and their performance for the three conditions (d'). The vertical axis represent the d' of the patient minus the mean d' of the control participants (to remove differences in difficulty between the tasks). The red line is the cut-off (-2SD of control participants' performance). The orange line is the corrected cut-off without the outlier control participant for the verbal task (d'=0.588, see Table 4). Finally, the numbers above or below graphic bars represent sizes of lesions (mL).

It is noteworthy that:

- *Deficits in any of the three STM tasks (words, tones, visual) can occur **after lesions in either hemisphere**.*
- *Deficits in any of the three STM tasks (words, tones, visual) can occur **after lesions in either anterior (insulo-frontal) regions or posterior (insulo-parietal) regions**.*
- *Amongst the **five patients with deficits in verbal STM** (P001, P003, P009, P011, P019), four of them (P001, P003, P011, P019) also had deficits in musical STM, and three of them (P009, P011 and P019) also in visual STM. P011 and P019 had deficits in all three tasks, with P019 having one of the largest lesions in our sample (but see P007). P009 had a deficit in auditory verbal memory but not musical memory (see also P020, with a score at cut-off for auditory verbal memory only). P003 who is the patient with the second largest deficit in verbal STM in the present sample only exhibited a small impairment for musical STM. Interestingly, P003's lesion encompassed left inferior parietal region, which are reported to be crucial for phonological STM (see Introduction).*
- *Amongst the **nine patients with deficits in musical STM** (P001, P002, P003, P008, P011, P014, P015, P018 and P019), four did not have any deficit in verbal and visual STM (P002, P008, P014, P018), and one had deficits in musical and visual STM but not verbal STM (P015).*
- *Three patients (P006, P009, P013) had **only a visual STM deficit**, including patients with left (P006) and right (P009 and P013) lesions and patients with anterior (P006 and P009) and posterior (P013) lesions.*

III. [§]Article 2 : "Recognition and intensity of musical emotions in brain-damaged patients: effect of lesion laterality"

Title: Recognition and intensity of musical emotions in brain-damaged patients: effect of lesion laterality

Authors: Catherine Hirel, Amy Belfi, Yohana Lévêque, Lesly Fornoni, Norbert Nighoghossian, Barbara Tillmann, Anne Caclin

A. Introduction

1. Musical emotions

Music is strongly connected to emotions. Listening to music activates areas well beyond the structures of the auditory cortex, such as frontal, temporal and parietal areas, limbic and para-limbic areas. These regions are involved in attention, working memory, episodic and semantic memory but also emotions. For example, a PET study on healthy subjects showed an increase of cerebral blood flow in the ventral striatum, amygdala, orbitofrontal cortex and medial ventral prefrontal cortex, while the subjects listened to music inducing chills. So, listening to music providing an intense emotion activates the same areas involved in emotions related to food, sex, drugs (1). Like for other rewards, dopamine is secreted by the striatum while listening to pleasant music (2). These emotions are essential for the social function of music.

Musical emotions can be impaired after brain damage. A patient with an isolated lesion of the amygdala had deficit of recognition of fearful and sad music (3). Another study on 16 patients with medial temporal lobectomy showed a deficit in recognition of both fearful faces and music (4).

It seems that musical emotions and musical perception are relatively dissociated. Cases of brain-damaged patients with musical anhedonia without perceptive deficit have been described in the literature (5,6). There are also many cases of acquired amusia without anhedonia. We also know that a stroke can cause acquired amusia with musical anhedonia (7).

[§] Article en cours de préparation

People with congenital amusia have difficulties of categorizing musical emotions but their emotional feeling remains intact (8,9). Finally, there are healthy subjects who have musical anhedonia, while their recognition of musical emotions is normal (10).

2. Facial emotions

We find in the literature more studies about facial emotion perception in brain-damaged patients than about musical emotions. A study using the "FEEL" test (Facially Expressed Emotion Labeling) on 24 stroke patients showed that the patients had lower performance than controls, especially for negative emotions (fear, anger, sadness, disgust). There was no difference between patients with right lesion and patients with left lesions (11). Other studies have shown a deficit in categorization of facial emotions in stroke patients (12–14). For example, a study on 60 stroke patients showed a deficit of recognition of facial emotions and prosodic emotions for patients with lesion of the right hemisphere, in comparison with controls (15).

The aim of this study was to investigate musical and facial emotions in brain-damaged patients. We compared musical perceptual performances, recognition of musical emotions and intensity of musical emotions in brain-damaged patients and control participants. We also used a facial emotions task to bring out more general difficulties, or specific deficits (e.g. deficit affecting only negative or positive emotions) observed in both sensory modalities.

B. Material and methods

1. Participants

The participants were 36 patients and 29 healthy subjects. Twenty-one of the patients were hospitalized in the stroke unit of the neurological hospital in Lyon, France. They presented an ischemic stroke in the right or left middle cerebral artery territory, confirmed by MRI. Inclusion criteria included having over eighteen years, having no other prior neurological or psychiatric disease, being native French-speaking, having no severe cognitive disorder, no severe hearing loss, being able to have a MRI and being able to be tested for 2 hours. Individuals were all tested in the chronic phase of their stroke (4-52 months after stroke). The same inclusion criteria were applied for 14 healthy subjects. All participants gave

written consent. The study was approved by the appropriate French ethics committee on Human Research (CPP Sud-Est III, 2014-050B).

Fifteen other patients were recruited in the Iowa (USA)[**], as well as 15 healthy subjects. Inclusion criteria included having over eighteen years, having no prior neurological or psychiatric disease, no history of alcohol or drug abuse, no visual or hearing impairments not fully corrected. The patients had focal brain damage due to stroke (n=8), surgical resection of a tumor (n=4), temporal lobectomy (n=3). All patients needed to be in the chronic epoch (at least three months post lesion onset).

2. Material

Music cognition was evaluated as a part of the neuropsychological assessment by using the MBEA (Montreal Battery of Evaluation of Amusia, (16)). The MBEA includes six subtests that measure different components of music cognition. The scale, contour, interval and rhythm subtests comprise 30 pairs of piano melodies, and the subject have to judge, on each trial, whether the two melodies sound the same or different. In the metric subtest, the subjects have to categorize the melodies either as a waltz or a march and in the memory subtest they have to determine if the melody is familiar from previous trials or not. This test allows us to diagnostic an eventual acquired amusia after brain damage. We also evaluated the pitch discrimination threshold, using a two-alternative forced choice task (17).

For the musical task, forty orchestrated musical excerpts of 20 seconds, coming from the Western classical repertoire, were used (8). Ten excerpts were related to joy, ten to sadness, ten to fear/anger and ten to serenity. After listening to each musical excerpt, participants had to judge what emotion it inspired them (only one possible response between the four emotions). Then, they were asked to rate the intensity of the evoked emotion on a subjective scale from 1 (weak) to 5 (strong).

For the visual task, forty black and white photos of faces expressing emotions were chosen from the study of Ekman & Frieser (18). Ten faces were related to joy, ten to sadness, ten to fear and ten were emotionally neutral. Neutrality was used instead of serenity, an emotion difficult to express and recognize on a face. Each face appeared on the screen for 2 seconds. Then participants had to choose the emotion evoked by the face, and they were asked to rate the intensity of the evoked emotion on the same subjective scale as for the music

[**] The study was in collaboration with Amy Belfi and Daniel Tranel, University of Iowa.

material, except for the cases when the participant answered "neutral" to the emotion recognition question, then no intensity rating was requested.

Presentation software (Neurobehavioral systems, Albany, CA, USA) was used to control the presentation of stimuli and record participants' responses given on the keyboard. Presentation order of music and face material was counter-balanced across participants.

3. Statistical analyses

For the demographical and the neuropsychological data (MBEA and PDT), we compared the three groups of participants (patients with left lesions, patients with right lesions and control participants) with ANOVAs. A Khi2 test was used to compare sex ratios.

For the emotion tasks, we computed, for each emotion and material (music and faces), the percentage of correct answers for categorization and the average rating of intensity for trials where the emotion was correctly recognized. Each dependant variable was analysed with a 3x4 ANOVA with Group (patients with left lesions vs. patients with right lesions vs. control participants) as the between-participants factor and Emotion (Joy, Sadness, Fear, Serenity/Neutral) as the within-participants factor. Post-hoc analyses for significant effects or interactions were carried out using a Fisher LSD test. For the rate of intensity for facial emotions, only three emotions were analysed (Joy, Sadness, Fear).

C. Results

1. Participants

Demographic data are presented in Table 1. Thirty-four patients and twenty-nine controls participants were included in the analyses: two patients were excluded from the analyses because they had a bilateral lesion. Among the 34 patients, 17 had lesions in the left hemisphere and 17 in the right hemisphere. About the nature of the lesion, 28 lesions were stroke, three lesions were temporal lobectomy for epilepsy and three lesions were tumor resections. The three groups were comparable for sex ratio, age, level of education and musical education.

MBEA

There was a difference between the two groups of patients and control participants for the MBEA score ($F(2,60)=3.3$; $p=0.045$). Post hoc analyses showed that control participants had a higher score than the patients with left lesions ($p=0.04$) and the patients with right lesions ($p=0.04$), and there was no difference between the two groups of patients ($p=0.9$).

The cut-offs (mean -2SD) were calculated from MBEA scores of 421 participants (http://www.brams.umontreal.ca/plab/publications/article/57#extras) (16). The cut-off score to be considered as amusic is $\leq 22.4/30$ for participants under sixty years, and $\leq 21.6/30$ for participants over sixty years. Based on these criterions, nine patients and two control participants were diagnosed as amusics. Among the nine patients, five had lesion in the right hemisphere and four had lesion in the left hemisphere.

PDT

There was no difference between the two groups of patients and control participants for the PDT ($F(2,45)=2.1$; $p=0.14$).

	Right lesions (n=17)	Left lesions (n=17)	Controls (n=29)	p (group effect)
Sex ratio M/F	6/11	10/7	12/17	p=0.35
Age (years)	55.9±11.1 (40-74)	61.4±11.5 (37-85)	58.4±9.7 (37-74)	p=0.33
Education (Years)	12.8±3.7 (5-18)	13.0±3.4 (5-16)	14.4±3.4 (5-20)	p=0.21
Musical education* (years)	0.8±2.3 (0-8)	5.3±13.5 (0-50)	3.8±9.4 (0-45)	p=0.48
PDT** (semi-tones)	1.5±1.3 (0.15-3.92)	1.35±1.5 (0.157-4.67)	0.8±0.9 (0.12-4.42)	p=0.14
MBEA score (/30)	23.5±2.8 (19.2-28.7)	23.6±3.1 (17.7-27.8)	25.2±2.0 (20.5-28.8)	**p=0.045**

Table 1: Demographic data and musical perception performances of patients and control participants.

For each parameter the group average, standard deviation and range is reported. Patients had a lower MBEA score in comparison with control participants

*Missing data for musical education for six patients and five control participants.

**Missing data for PDT for thirteen patients and two control participants.

2. Emotion tasks

Musical emotions

For performance for categorization of musical emotions, the ANOVA revealed a significant main effect of Emotion ($F(3,180)=20.5$; $p<0.0001$). Post hoc analyses showed that joy and fear were easier to categorize than sadness and serenity ($p<0.0001$). There was a significant main effect of Group ($F(2,60)=4.8$; $p=0.01$). Post hoc analyses showed that patients with left lesions had lower performance than control participants ($p=0.026$). There was no difference between the two groups of patients ($p=0.42$) and between patients with right lesions and control participants ($p=0.19$). There was no significant interaction between the factors Group and Emotion ($F(6,180)=0.5$; $p=0.78$).

For ratings of intensity of musical emotions, one patient (right lesion) was excluded from the analysis because of an absence of correctly identified emotion for sad musical excerpts. The ANOVA revealed a significant main effect of Emotion ($F(3,177)=5.0$; $p=0.002$). Post hoc analyses showed that happy excerpts were rated higher than excerpts of the three other emotions ($p\leq0.01$). There was no effect of Group ($F(2,59)=0.6$; $p=0.58$). There was a significant interaction between the factors Group and Emotion ($F(6,177)=2.5$; $p=0.02$). Post hoc analyses showed that patients with right lesions rated joy and serenity higher than sadness and fear ($p<0.003$), whereas no such pattern was observed in the other two groups. Controls rated joy higher than sadness and serenity ($p<0.008$). Patients with right lesions rated fear significantly lower than control participants ($p=0.02$), and marginally lower than patients with left lesions ($p=0.09$).

Facial emotions

For performance for categorization of facial emotions, the ANOVA revealed a significant main effect of Emotion ($F(3,180)=34.3$; $p<0.0001$). Post hoc analyses showed that joy and fear were easier to categorize than sadness and neutral faces ($p<0.0001$). There was no effect of Group ($F(2,60)=0.37$; $p=0.7$). There was no interaction between the factors Group and Emotion ($F(6,180)=1.7$; $p=0.12$).

About ratings of intensity of facial emotions, the ANOVA revealed a significant main effect of Emotion ($F(2,120)=45.8$; $p<0.0001$). Post hoc analyses showed that sadness was rated lower than joy and fear ($p<0.0001$). There was no effect of Group ($F(2,60)=0.09$;

p=0.9). There was no interaction between the factors Group and Emotion (F(4,120)=1.1 ; p=0.34).

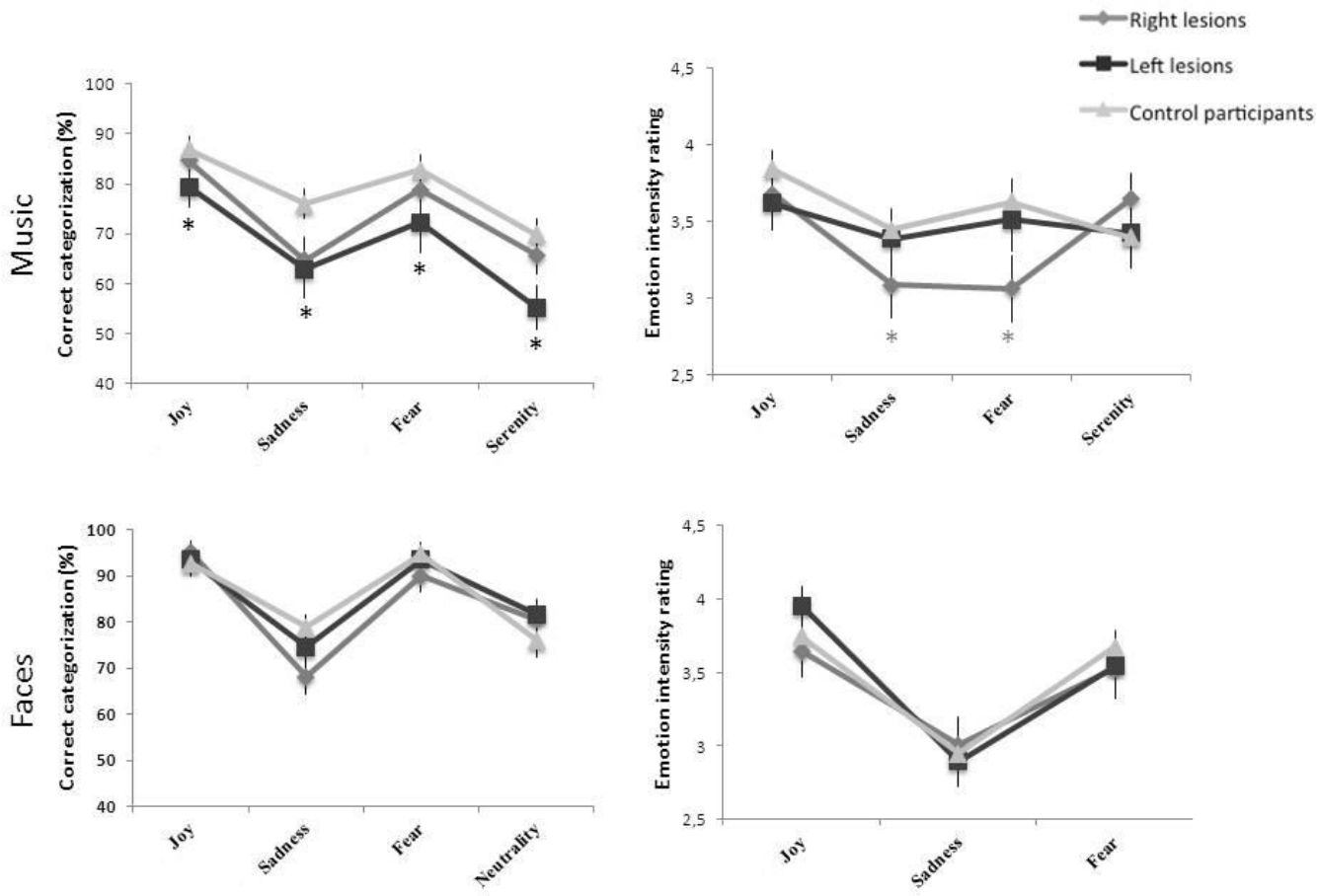

Figure 1: Performance of patients and control participants for categorization of musical and facial emotions, and emotion intensity rating.

In the left: percentage of correct categorizations in the music and the face emotion categorization tasks. In the right: mean emotion intensity rating of patients and control groups on a scale from 1 (weak) to 5 (strong), in the music and the face tasks.

Patients with left lesions had lower performance for categorization of musical emotions, in comparison with control participants. Patients with right lesions rated joy and serenity higher than sadness and fear.

3. Correlations

There was a positive correlation between MBEA mean score and percentage of correct categorization of musical emotions (p<0.0001). There was no correlation between MBEA mean score and percentage of correct categorization of facial emotions (p=0.069).

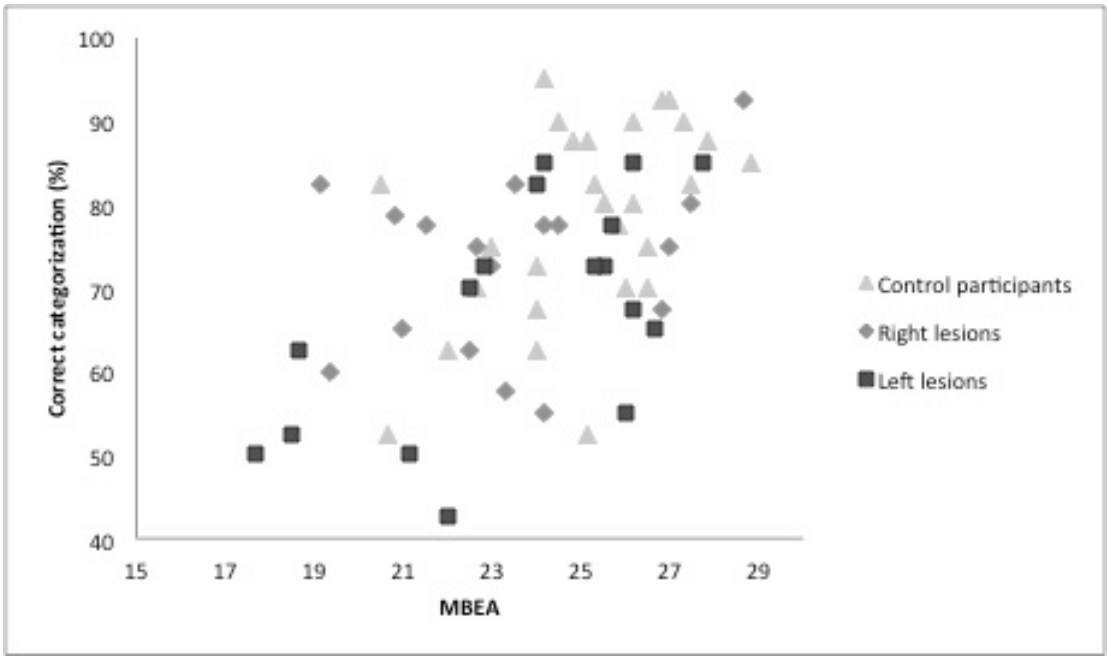

Figure 2: Scatter plot: Correlation between MBEA score and percentage of correct categorization of musical emotions

There is a significant relation between the performance for the MBEA and categorization of musical emotions.

4. Individual results

Only one patient had a deficit in categorization of facial emotions. It's a 59-year-old female. She had difficulty to categorize sadness and fear for music (50% and 40% of correct answers respectively versus 80% for happiness and 90% for serenity) and faces (40% and 50% of correct answers respectively versus 80% for happiness and 90% for neutral). She had an acquired amusia (MBEA mean score 21/30), without musical anhedonia, and an elevated PDT (3.92 semi tones). She had a stroke in the right hemisphere, damaging the basal ganglia (striatum). The two other patients with lesion in the right basal ganglia had a deficit to recognize sad music only.

For the individual results, the cut-offs are defined as below 2SD from the mean of control participants' performance. Among the eleven amusic participants (nine patients and two control participants, the latter thus being congenital amusics), four had a deficit in categorization of musical emotions (three patients and one control participant) and none had deficit in categorization of facial emotions. Three patients and one control participant had a

deficit in categorization of musical emotions, without amusia. One patient had acquired amusia with musical anhedonia (strongly diminished ratings for emotion intensity), without deficit in categorization of musical emotions (for details about this patient, see (7)).

D. Discussion

The present study investigated musical and facial emotions in brain-damaged patients, with a majority of stroke cases. The participants had to categorize the emotion of musical excerpts or faces and rate the intensity of the emotion. Performance in the musical emotion recognition test was found to be significantly lower in patients with left lesions in comparison with control participants. There was no difference between the two groups of patients for emotion categorization. Patients with right lesions rated the emotional intensity of music lower for sadness and fear than for joy and serenity. There was no difference for faces emotions (categorization or intensity) between patients and control participants.

1. Euphoric mood after right lesions

There are two main theories about the lateralization of processing emotions in the brain. The Right Hemisphere Hypothesis (RHH) suggests that emotion is processed predominantly in the right hemisphere, regardless of valence (14,19). The Valence Hypothesis (VH) suggests that the left hemisphere processes positive emotions, while the right hemisphere processes negative emotions. In 1982, a review showed that right lesions were associated to pathological laughing and euphoric mood change, while pathological crying was associated with predominantly left-sided lesions (20). A meta-analyse of studies implying facial emotions showed that right-sided lesions were associated with perception deficits of negative emotions, more marked than positive emotions (21). Other studies have found no difference between the two hemispheres regarding valence (11,12,15).

Most of studies about emotions after brain damage involved perception tasks of emotions on facial stimuli. We found no difference between the patients and control participants on the facial task, perhaps because the task was rather easy. During the musical task, patients with right lesions rated the emotional intensity of music lower for sadness and fear than for happy and serenity, compatible with a euphoric mood. Patients with left lesions had lower performance than control participants to categorize the emotions, while there was no difference between the two groups of patients. So, our results are not in favour of the

RHH, but rather in favour of the VH. Other studies are necessary to conclude between the VH and the RHH. It is noteworthy here that the difference between the two patient groups emerge only in the analysis of intensity ratings, and not in categorizations. It suggests that a conceptual knowledge about emotion categories can persist whereas emotions are only abnormally felt by the patient.

2. Patterns of musical deficits after brain damage

There was a positive correlation between MBEA mean score and percentage of correct categorization of musical emotions. These results are concordant with a study on congenital amusia (8) showing that congenital amusics have a lower performance musical emotion categorization than control participants. These findings reveal that pitch deficits can hinder to some extent the recognition of emotions conveyed by musical pieces. But among our stroke patients, some developed acquired amusia with or without deficit in categorization of musical emotions and some patients had a deficit in categorization of musical emotions without amusia. We also had one patient with acquired amusia and musical anhedonia, without deficit in categorization of musical emotions (7). It seems that focal lesions lead to deficits more various than congenital amusia, and the variety of profiles observed among the present patients sample are in keeping with the hypothesis of (at least partly) separate processes for music perception and emotion.

We saw in the individual results that patients with lesions in the right basal ganglia had a deficit to categorize negative emotions (sadness and fear) on faces and music. Another study on facial emotions recognition showed that patients with localized basal ganglia damage performed significantly worse in recognizing negative emotions than the controls (anger, disgust and fear) and patients with localized thalamic damage performed significantly worse in recognizing sadness than the controls (13). Our results are consistent with these findings.

Our results showed a variety of deficits in musical emotions after brain damages. More studies should confirm these results. In particular, imaging studies could help us to determine which cerebral areas are involved in the recognition of musical emotions and in the intensity of these emotions.

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IV. ††Article 3 : "Amusie acquise et anhédonie musicale"

Titre : Amusie acquise et anhédonie musicale

Auteurs : Catherine Hirel[a], Yohana Lévêque[bcd], Gianluca Deiana[e], Nathalie Richard[f], Tae-Hee Cho[a], Laura Mechtouff[a], Laurent Derex[a], Barbara Tillmann[cd], Anne Caclin[bd], Norbert Nighoghossian[a]

Affiliations :

[a]Service de neurologie vasculaire, Hôpital Neurologique Pierre-Wertheimer, hospices civils de Lyon, Université Lyon-I, 59, boulevard Pinel, 69677 Bron, France

[b]INSERM, U1028; CNRS, UMR5292; Centre de Recherche en Neurosciences de Lyon, Equipe Dynamique cérébrale et Cognition, Lyon, F-69000, FranceFrance

[c]CNRS, UMR5292; INSERM, U1028; Centre de Recherche en Neurosciences de Lyon, Equipe Cognition Auditive et Psychoacoustique, Lyon, F-69000, France

[d]Université Lyon 1, Lyon, F-69000, France

[e]Service de Neuro-radiologie, Hôpital Neurologique Pierre-Wertheimer, hospices civils de Lyon, universite Lyon-I, 59, boulevard Pinel, 69677 Bron, France

[f]Centre de Neuroscience Cognitive, UMR 5229, CNRS, 67, Boulevard Pinel, 69675 BRON, Cedex, France

Résumé :

L'amusie est définie comme une agnosie auditive spécifique à la musique, consécutive à une lésion cérébrale, ou congénitale. Elle est parfois associée à une anhédonie musicale, dont les corrélations anatomo-cliniques sont mal connues. Nous rapportons ici le cas d'un patient de 43 ans ayant présenté en janvier 2012 un accident ischémique cérébral sylvien droit affectant principalement le cortex temporal supérieur, notamment la partie latérale du Gyrus de Heschl et la partie postérieure du gyrus temporal supérieur (aires 21 et 22 de Brodmann). Les tests neuropsychologiques retrouvaient une amusie associée à une anhédonie musicale. L'amusie symptomatique d'une lésion temporale droite est classique, toutefois elle est exceptionnellement associée à une anhédonie musicale. Cette observation pose la question des relations entre les réseaux cérébraux impliqués dans le traitement de la perception musicale et des émotions musicales.

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A. Introduction

L'amusie est définie comme une agnosie auditive consécutive à une lésion cérébrale ou d'origine congénitale. Elle s'exprime selon plusieurs modalités : amusie réceptive ou expressive, alexie musicale, amnésie musicale ou instrumentale, agraphie musicale, troubles du rythme (1). L'amusie acquise est le plus souvent la conséquence d'une lésion vasculaire ischémique ou hémorragique. Elle est plus fréquente et sévère en présence de lésions de l'hémisphère droit (2). Ce symptôme fait rarement l'objet d'une plainte spontanée et reste peu documenté à l'issue d'un accident vasculaire cérébral. Par ailleurs, les procédures utilisées pour diagnostiquer l'amusie n'incluent généralement pas l'évaluation des émotions musicales. L'amusie semble rarement associée à une perte des émotions musicales ou de l'appréciation de la musique (3,4). Inversement, quelques cas isolés d'anhédonie musicale sans atteinte de la perception de la musique ont été rapportés, suite à des lésions du système limbique (5) ou du lobe pariétal droit (6). Nous rapportons ici l'association exceptionnelle des deux syndromes.

B. Observation

Un patient âgé de 43 ans, droitier, cadre commercial, amateur de musique, fut hospitalisé le 30 janvier 2012 en raison de l'installation brutale d'une maladresse du membre supérieur gauche associée à une dysarthrie. A l'admission, l'examen neurologique décelait une hémianopsie latérale homonyme gauche et une dysarthrie. L'IRM en séquence de diffusion (DWI) objectivait une souffrance ischémique du territoire sylvien postérieur droit symptomatique d'une occlusion du segment M2 de l'artère cérébrale moyenne droite. Un traitement par thrombolyse intraveineuse (rt-Pa) fut administré 4 heures après le début des symptômes. L'évolution fut favorable. Le bilan étiologique révéla un foramen ovale perméable, la recherche d'une prise de toxique était négative. Un traitement anti-agrégant plaquettaire fut prescrit.

Lors d'une consultation le 11 juillet 2012, le patient rapportait spontanément une perte d'intérêt pour la musique, et notamment une perte des émotions qu'il ressentait auparavant lors de l'écoute de la musique. Le patient n'était pas déprimé à l'interrogatoire ainsi qu'en regard du score à l'échelle d'Hamilton. Le patient ne signalait pas d'anhédonie dans d'autres secteurs tels que les arts, le goût ou les odeurs. L'anhédonie affectait sélectivement la musique.

Le caractère inhabituel de la plainte entraîna une série d'explorations neuro-psychologiques orientées sur les perceptions musicales et le ressenti émotionnel, menées les 18 avril et 13 mai 2013. Préalablement à la réalisation de ces tests, un examen de l'audition révéla une perte auditive moyenne sur les hautes fréquences (>2000Hz), n'expliquant pas la plainte, et les potentiels évoqués auditifs étaient normaux.

La perception musicale fut évaluée à l'aide des six tests de la batterie MBEA (Montréal Battery for the Evaluation of Amusia, (7)). Dans les quatre premiers tests, le sujet compare des paires de mélodies et doit détecter successivement des changements de tonalité, de contour mélodique, d'intervalle et de rythme. Le cinquième test évalue la reconnaissance de la métrique (valse ou marche) et le dernier test la mémoire incidente. Le score moyen MBEA du patient était de 21.3/30 (inférieur à la valeur limite en-dessous de laquelle le participant est considéré comme amusique : 23/30), avec un score pathologique dans les tests de tonalité, intervalle et métrique, confirmant une amusie. La discrimination fréquentielle fine fut évaluée à l'aide d'un seuil de discrimination (8), et était comprise dans la norme (seuil à 0.31 demi-ton).

L'étude de la perception des émotions dans la parole, effectuée à l'aide de la batterie MEC (Montréal Evaluation de la Communication, (9)), n'objectiva pas d'altération de la reconnaissance des intonations, ni pour la prosodie linguistique (question/affirmation/ordre), ni pour la prosodie émotionnelle (triste/heureux/fâché), avec respectivement un score de 11/12 et 12/12. L'analyse de la perception des émotions fut complétée par une tâche de catégorisation d'émotions, accompagnée d'un jugement de l'intensité de ces émotions, à partir d'extraits musicaux (10), et d'un matériel visuel, les visages d'Ekman (11). Le patient devait identifier l'émotion exprimée par chaque item (Joie, Tristesse, Peur, Sérénité pour la musique, et Joie, Tristesse, Peur, Neutralité pour les visages) puis coter l'intensité de l'émotion sur une échelle de 1 à 5 (de faible à fort). Les scores du patient sont présentés sur la figure 1, en parallèle avec un sujet témoin non-musicien apparié en sexe, âge et niveau d'étude. La catégorisation des émotions par le patient était normale, tant pour les visages que pour les extraits musicaux. En revanche, si l'intensité du ressenti émotionnel était normale pour les visages, elle était très atténuée pour la musique, en accord avec la plainte du patient. En conclusion, le patient présentait une amusie acquise associée à une sévère altération des émotions musicales définissant l'anhédonie.

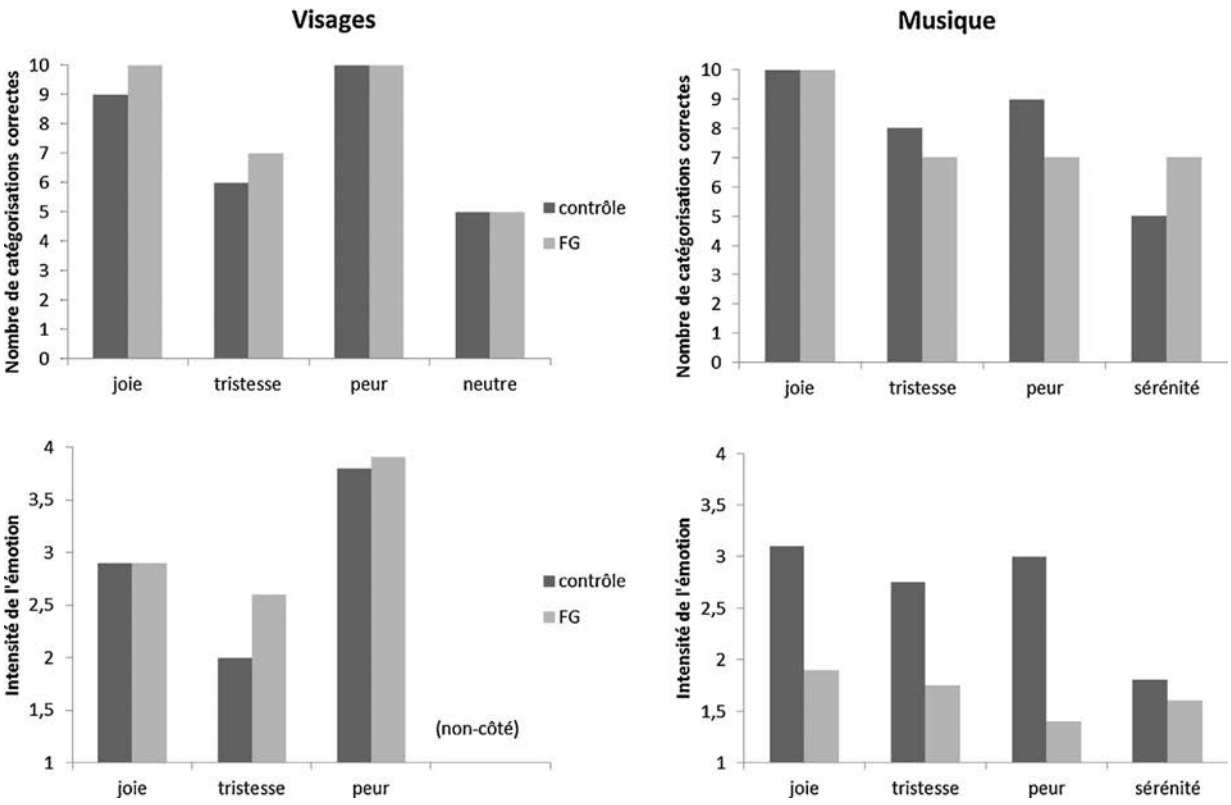

Figure 1 : *Analyse descriptive. Gauche : étude des émotions sur les visages (40 visages de Ekman, 10 par émotion, (11)), avec catégorisation (Joie/Tristesse/Peur/Neutre) et ressenti des émotions sur une échelle de 1 (faible) à 5 (fort), par le patient (F.G.) et un témoin apparié.*
Droite : étude des émotions sur les musiques au piano (40 extraits, 10 par émotion, (10)) avec catégorisation (Joie/Tristesse/Peur/Sérénité) et ressenti des émotions sur une échelle de 1 (faible) à 5 (fort), par le patient (F.G.) et un témoin apparié.

L'analyse neuropsychologique fut complétée par la réalisation d'une imagerie par IRM à haut champ (Philips Achieva 3T), 18 mois après la constitution de la lésion. Une acquisition 3D FLAIR avec rendu de volume a été réalisée (Figure 2). La lésion a été comparée à un atlas de référence (12). La lésion affectait les aires 22, 21, 38, 42 et 41 de Brodmann. Un rendu en trois dimensions de la lésion, du noyau amygdalien, de l'insula et du cortex auditif primaire fut réalisé grâce au logiciel BrainVisa (http://brainvisa.info/index_f.html) (Figure 3). La lésion était principalement localisée dans la partie postérieure du gyrus temporal supérieur (BA22), elle s'étendait latéralement au cortex auditif primaire (BA41 et 42) et au segment ventral du gyrus temporal moyen (BA 21).

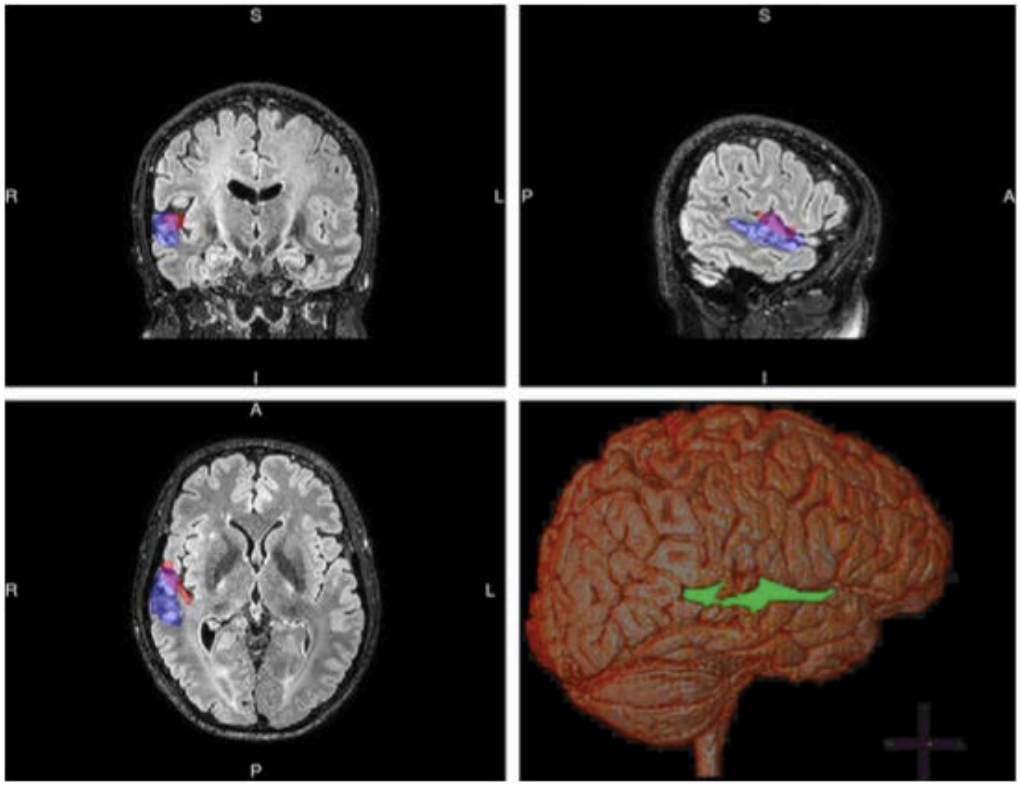

Figure 2 : *La séquence FLAIR (Fluid-Attenuated Inverse Recovery, pondération T2) utilise le temps echo (TE): 1.8 ms, temps inversion (TI): 353 ms, temps repetition (TR): 5000 ms, angle retourné 180, longueur du train echo: 221, taille voxel 0.5 x 0.5 x 1.0 mm. La lésion apparaît en violet et le gyrus de Heschl en rose sur les 3 premières images. La 4ème image est une reconstruction 3D, où la lésion apparaît en vert.*

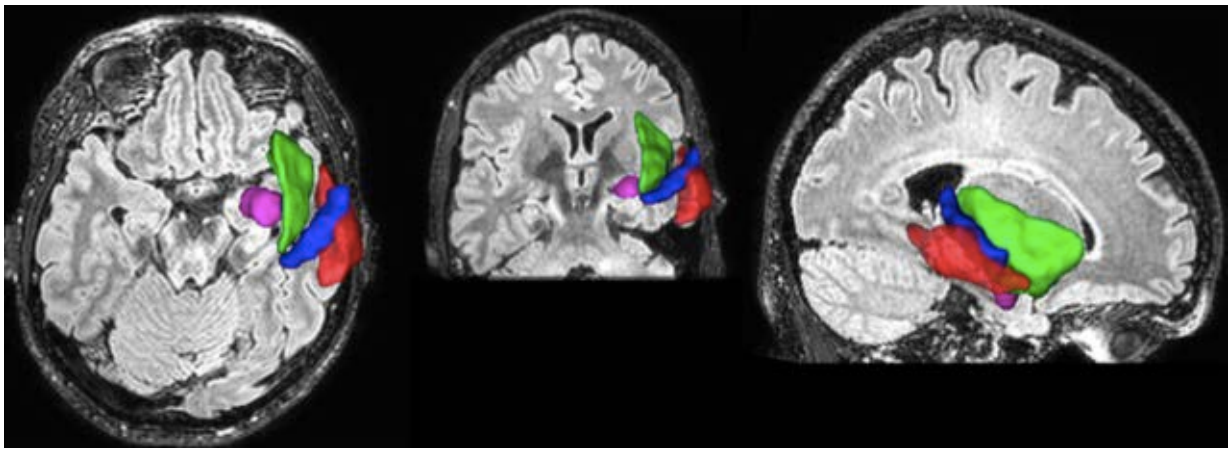

Figure 3 : *La représentation 3D de la lésion (rouge), de l'amygdale (rose), de l'insula (vert) et du gyrus de Heschl (bleu) a été créée avec le logiciel Brainvisa, en coupes frontale, sagittale et axiale.*

C. Discussion

Les données relatives aux émotions musicales dans l'amusie post-lésionnelle sont rares. L'amusie observée à l'issue d'un accident ischémique cérébral est le plus souvent associée à des troubles cognitifs d'ordre mnésiques ou dysexécutifs (13). L'association amusie–anhédonie fonde le caractère exceptionnel de notre observation. De plus, l'érosion affective de ce patient pour la musique contrastait avec la préservation de son aptitude à catégoriser sans difficulté l'émotion qu'un extrait musical devrait susciter.

L'étude des réseaux cérébraux sous-tendant la perception musicale a largement bénéficié de la tomographie d'émission de positons et de l'IRM fonctionnelle (14). La perception et la mémoire des hauteurs et des mélodies recrutent les aires auditives temporales et le gyrus frontal inférieur, avec une prédominance de l'hémisphère droit, et l'amusie congénitale semble liée à un déficit fonctionnel de ce réseau (15). Au-delà de ce réseau fronto-temporal, la perception musicale recrute un réseau cortical et sous-cortical, impliquant particulièrement le cortex prémoteur dans la perception du rythme (16).

L'imagerie cérébrale fonctionnelle a également permis d'étudier les réseaux cérébraux impliqués dans le ressenti d'émotions musicales (14). Les régions concernées sont en particulier les structures limbiques impliquées dans la sensation de plaisir et de récompense, principalement le striatum ventral, le mésencéphale, l'amygdale, le cortex orbito-frontal et le cortex pré-frontal ventral médial (17). Une étude en IRM fonctionnelle intégrant des stimuli musicaux, réalisée chez des patients présentant une anhédonie, a également montré une réduction d'activation des aires limbiques et para-limbiques impliquées dans le traitement de la récompense (18).

Dans notre cas, l'association d'une amusie associée à une anhédonie musicale consécutive à une lésion temporale droite, en l'absence de lésion affectant le système limbique, invite à discuter les liens existant entre les réseaux respectivement engagés dans la perception et les émotions musicales. Dans ce cadre, Salimpoor et al. ont montré que la connectivité fonctionnelle entre les régions auditives du gyrus temporal supérieur et le noyau accumbens, élément du système limbique, prédisait le jugement émotionnel des sujets évaluant des stimuli musicaux (19). Les données rapportées dans notre cas suggèrent une entrée défaillante dans ce réseau cortico-striatal en lien avec la lésion temporale. La dissociation entre perception et émotion en matière musicale a récemment été observée chez des sujets sains (20), ce qui conforte la notion d'un traitement sélectif.

Conflits d'intérêt :

Les auteurs déclarent ne pas avoir de conflit d'intérêt en relation avec cet article.

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V. Conclusion

Les atteintes neuropsychologiques après un accident vasculaire cérébral sont fréquentes et peuvent avoir des conséquences importantes sur la qualité de vie des patients. La musique est universelle, présente depuis la naissance chez tous les humains, et apporte un bien-être moral. L'objectif de ce travail de thèse était de caractériser les déficits auditifs pouvant survenir après un accident vasculaire cérébral, et notamment ceux concernant la musique. Pour cela, nous avons recruté 20 patients ayant été pris en charge à l'unité neuro-vasculaire de l'hôpital neurologique de Bron pour un accident ischémique cérébral dans le territoire de l'artère sylvienne droite ou gauche et 14 sujets contrôles. Les participants ont réalisé un bilan neuropsychologique comprenant le MBEA (une batterie de tests permettant de diagnostiquer une amusie acquise), une tâche de mémoire à court terme auditive verbale et musicale, avec une tâche visuelle de contrôle, et enfin une tâche de catégorisation et cotation de l'intensité d'émotions musicales ou sur des visages. Concernant la tâche de mémoire à court terme auditive, une analyse complémentaire d'imagerie a été réalisée par la technique du Voxel-based Lesion Symptom Mapping (VLSM).

Parmi les vingt patients, trois présentaient une amusie acquise, tous ayant une lésion dans l'hémisphère gauche. D'autres études ont montré que l'amusie acquise peut survenir après des lésions de l'hémisphère gauche ou droit. Les patients avaient des performances moins bonnes que les participants contrôle pour la tâche de mémoire à court terme, quel que soit le matériel utilisé (auditif verbal, auditif musical, visuel). Nos résultats sont en faveur de l'implication des deux hémisphères dans la mémoire à court terme auditive. Les résultats individuels montraient une double dissociation avec des patients présentant un déficit en MCT auditive verbale et des performances normales en MCT auditive musicale, et inversement. Cela est en faveur de réseaux neuronaux dissociés pour le traitement de la musique et du langage, et est concordant avec la littérature. Les résultats des analyses en VLSM ont montré l'importance de l'opercule fronto-pariétal inférieur dans la MCT. Cela pourrait être en lien avec une déconnection de la voie dorsale, comprenant le faisceau arqué.

La tâche sur les émotions musicales a également été réalisée par quinze patients américains et quinze sujets contrôles appariés. Les patients avec une lésion de l'hémisphère gauche avaient de moins bonnes performances en catégorisation des émotions musicales par rapports aux sujets contrôle. Les patients avec une lésion de l'hémisphère droit cotaient l'intensité de la peur et de la tristesse plus faiblement que la joie et la sérénité. Il n'y avait pas

de différence entre les trois groupes de participants pour les émotions sur les visages. Dans la littérature, il est rapporté un déficit de reconnaissance des émotions sur les visages après un AVC, et quelques études ont montré l'implication de l'amygdale et du lobe temporal dans la reconnaissance des musiques inspirant la peur et la tristesse. Nos résultats sont à confirmer par d'autres études, et ne permettent pas de trancher entre les deux hypothèses : l'hypothèse de "la valence", affirmant que l'hémisphère droit est impliqué dans les émotions négatives et l'hémisphère gauche dans les émotions positives, et l'hypothèse de "l'hémisphère droit", affirmant que l'hémisphère droit est responsable du traitement des émotions.

Nous avons rapporté le cas de F.G., un patient de 43 ans ayant présenté une amusie acquise associée à une anhédonie musicale marquée, sans déficit de catégorisation des émotions musicales, après un infarctus temporal droit. Cette association est rare. Des cas d'anhédonie musicale sans amusie ont été également rapportés.

La principale limite de ce travail est le nombre limité de patients recrutés, les résultats devront être confirmés par des études comportant un nombre de patients plus important. Notamment pour l'analyse en VLSM, nous avons dû superposer les lésions sur un seul hémisphère et nous n'avons donc pas pu conclure sur l'implication de chaque hémisphère dans le traitement de la mémoire à court terme auditive. Les deux tâches de MCT auditive n'étaient pas de même difficulté, ce qui peut également entraîner un biais.

L'intérêt de ce travail est double. Sur le plan scientifique, il nous a permis d'avancer sur la compréhension des mécanismes du traitement cérébral de la musique et du langage. Les résultats sont en faveur de réseaux neuronaux en partie dissociés pour la musique et le langage.

Sur le plan clinique, ce travail permet de mettre en évidence des déficits neuropsychologiques peu connus en pratique clinique, et notamment dans les unités neuro-vasculaires. Il faut questionner les patients en consultation de suivi post AVC sur les changements éventuels à l'écoute de la musique, car les plaintes spontanées sont rares. Si le patient rapporte une baisse du plaisir à l'écoute de la musique, il convient de réaliser un questionnaire de dépression, pour éliminer une anhédonie plus générale en lien avec un syndrome dépressif, fréquent après un AVC. Le bilan neuropsychologique pourra être orienté en fonction des plaintes du patient et des symptômes retrouvés à l'interrogatoire. Mais il faut tout d'abord valider des tests spécifiques. Nous proposons ici une batterie de tests permettant de diagnostiquer une amusie acquise, un déficit en MCT auditive et un déficit concernant les

émotions musicales. Des techniques de rééducation de ces troubles doivent être validées, pour limiter l'impact qu'ils peuvent avoir sur la qualité de vie des patients.

THESE SOUTENUE PAR Mme Catherine Hirel

CONCLUSIONS

Les conséquences neuro-psychologiques des accidents vasculaires cérébraux (AVC) sont très importantes sur la vie sociale, personnelle et professionnelle des patients. Les séquelles affectant l'audition, et notamment la perception musicale, sont peu documentées. L'objectif de ce travail de thèse était de caractériser les déficits auditifs affectant les patients après un accident ischémique cérébral dans le territoire de l'artère cérébrale moyenne droite ou gauche. Des tâches de perception musicale, de mémoire auditive à court terme (verbale et musicale), de catégorisation des émotions et de ressenti émotionnel (musiques) ont été réalisées par des patients cérébro-lésés et des sujets contrôles. Les résultats comportementaux ont été complétés par une analyse en Voxel-based Lesion Symptom Mapping (VLSM) pour la tâche de mémoire à court terme (MCT).

Une amusie acquise a été détectée chez certains patients, quelle que soit la latéralité de la lésion. En moyenne, les patients présentaient un déficit en MCT par rapport aux sujets contrôles, quel que soit le matériel utilisé (auditif verbal, auditif musical, ou visuel). Les résultats individuels montraient une double dissociation au sein de la modalité auditive, avec certains patients présentant un déficit en MCT verbale, sans déficit en MCT musicale, et inversement. L'étude des émotions musicales a mis en évidence un déficit de catégorisation des émotions musicales chez les patients avec une lésion de l'hémisphère gauche, et un ressenti émotionnel plus faible pour la tristesse et la peur par rapport à la joie et la sérénité chez les patients avec une lésion de l'hémisphère droit. Nous rapportons le cas d'un patient présentant une amusie acquise associée à une anhédonie musicale prononcée dans les suites d'un infarctus temporal droit.

Les déficits auditifs après un AVC sont donc nombreux et peuvent s'associer. Il est important de les dépister grâce à des tests neuropsychologiques validés.

Vu, Le Doyen de la Faculté
de Médecine et de Maïeutique
Lyon-Sud Charles Mérieux

Carole BURILLON

Le Président de la Thèse
Pr Norbert NIGHOGHOSSIAN

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Pierre Coulet

HIREL Catherine

Déficits auditifs après un accident vasculaire cérébral : Perception, mémoire et émotions musicale

12 fig., 7 tabl.

RESUME

L'objectif de ce travail de thèse était de caractériser les déficits auditifs musicaux affectant les patients après un accident ischémique cérébral. Des tâches de perception musicale, de mémoire auditive à court terme (verbale et musicale), de catégorisation des émotions et de ressenti émotionnel (musiques) ont été réalisées par des patients cérébro-lésés et des sujets contrôles. Les résultats comportementaux ont été complétés par une analyse en Voxel-based Lesion Symptom Mapping (VLSM) pour la tâche de mémoire à court terme (MCT).

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MOTS CLES

-Accident vasculaire cérébral
-Amusie
-Mémoire à court terme
-Emotions
-Perception auditive

JURY

Président : Pr Norbert NIGHOGHOSSIAN
Membres : Pr Alain VIGHETTO
Pr Jacques LUAUTE
Dr Anne CACLIN

DATE DE SOUTENANCE

7 octobre 2016

ADRESSE DE L'AUTEUR

4, place des Célestins. 69002 Lyon