Frontal cortical lesions and their effect on the control of memory retrieval and general tests of executive functions

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Abstract

Many major claims about the functions of the frontal cortex originate from patient studies examining the effects of extensive damage to the anterior part of the brain, including subcortical and extra-frontal regions. In general, the claims are that damage to the frontal cortex results in generalized impairments of executive functions that can be measured by specific tests or observed in specific behaviours. However, the attribution of deficits to the frontal cortex per se based on examination of patients with anterior brain damage that includes massive extra-frontal damage is a serious problem leading to potentially incorrect interpretation of frontal cortical function. This thesis tested the validity of some of these claims about frontal cortical functions by examining the performance of patients with well-documented lesions restricted to the frontal cortex and contrasting it with that of patients with temporal lobe lesions and neurologically intact individuals matched for age and education.. The patients had undergone brain surgery at the Montreal Neurological Hospital for the removal, in the frontal cortex, of a low-grade cerebral tumour or cortical excision for the relief of focal epileptic seizures. A few patients had damage following a stroke.

Study 1 showed that the Frontal Assessment Battery (FAB; Dubois et al., 2000), which is a short battery assumed to be a sensitive measure of frontal cortex executive dysfunction, but only validated on patients with a variety of neurodegenerative conditions causing widespread brain damage, is not a sensitive measure of frontal cortex executive dysfunction. Only performance on the verbal fluency subtest was specifically sensitive to damage to the frontal cortex, more specifically to the left dorsomedial frontal cortex. In Study 2, the presence of

utilization behaviour (Lhermitte, 1983), defined as the impulse to grasp and use a presented object although it is not contextually appropriate to use it that has been commonly attributed to the frontal cortex, did not differ in patients with frontal cortical lesions in comparison with patients with temporal lobe lesions and normal control subjects. These results suggest that, in previous studies, the impairment on the FAB and the exhibition of utilization behavior by patients may have been due to widespread brain dysfunction or to frontal cortical damage in conjunction with other damage, but not solely to frontal cortical damage.

In addition, the claim that memory for context depends on the frontal cortex only under certain circumstances, such as when memory traces require active disambiguation (Petrides, 2002, 2005) was examined. Subjects performed a mnemonic context retrieval task in which the stability with which items (words) and contexts (abstract coloured backgrounds) entered in relationships with one another was manipulated in order to recruit disambiguation processes (Study 3). Patients with lesions to the left dorsomedial frontal cortex were impaired mnemonic context retrieval, regardless of the stability of the relationships between items and contexts. In contrast, lesions to the right ventrolateral prefrontal cortex caused impairment only on when the relationships between items and contexts were unstable, suggesting that this region is critical for active retrieval processes (Petrides, 2002, 2005) necessary to disambiguate information existing in multiple and unstable ways in memory during context retrieval.

In conclusion, the lesion specificity and the inclusion of patient and normal control groups in the present work demonstrated that no generalized executive or behavioural impairments, as measured by the FAB and observed in

utilization behaviour, result from lesions restricted to the frontal cortex, but that precise regions of the frontal cortex contribute specifically to particular cognitive processes.

Résumé

Plusieurs affirmations importantes au sujet des fonctions du cortex frontal émanent d'études de patients présentant de larges lésions s'étendant à toute la portion antérieure du cerveau, incluant des structures sous-corticales et extra-frontales. Ces affirmations prétendent que les lésions au cortex frontal sont à l'origine de déficits généralisés des fonctions exécutives pouvant être mesurés par des tests spécifiques ou observés par des comportements particuliers. Cependant, l'attribution de ces déficits au cortex frontal sur la base d'études de patients avec des lésions cérébrales s'étendant hors du cortex frontal est un problème sérieux pouvant mener à une interprétation potentiellement erronée des fonctions corticales frontales. Les présentes expériences ont tenté de tester la validité de certaines de ces affirmations en étudiant des patients présentant des lésions bien définies et limitées au cortex frontal et en les comparant à des patients avec des lésions au lobe temporal et à des sujets sains sans atteinte neurologique, appariés selon l'âge et l'éducation. Les patients étudiés avaient subi une chirurgie cérébrale à l'Hôpital Neurologique de Montréal pour l'exérèse d'une tumeur cérébrale de bas grade ou l'ablation corticale d'un foyer épileptique. Quelques patients présentaient un dommage cérébral suite à un accident vasculaire cérébral.

L'Étude 1 a démontré que la Batterie Rapide d'Efficience Frontale (BREF; Dubois et al., 2000), réputée comme étant un outil de mesure sensible à une dysfonction exécutive du cortex frontal, mais ayant été validée uniquement avec des patients présentant différentes conditions neurodégénératives causant des lésions cérébrales étendues à tout le cerveau, n'est pas une mesure sensible à une dysfonction corticale frontale. Seulement la performance au sous-test de fluence

verbale phonémique était sensible à une lésion au cortex frontal dorsomédial gauche. Dans l'Étude 2, aucune différence n'a été révélée quant à la présence du comportement d'utilisation d'objets, défini par Lhermitte (1983) comme l'impulsion de saisir et utiliser un objet présenté malgré que le contexte ne s'y prête pas et attribué au cortex frontal, entre les patients avec des lésions au cortex frontal, les patients avec des lésions temporales et les sujets sains. Ces résultats suggèrent que, dans les études antérieures, les déficits à la BREF et la manifestation de comportements d'utilisation pourraient avoir résulté du dommage cérébral généralisé ou des lésions au cortex frontal conjointement au dommage aux autres régions, mais n'auraient pas résulté uniquement des lésions au cortex frontal.

Finalement, une troisième affirmation au sujet des fonctions corticales frontales, soit que la mémoire pour le contexte dépende du cortex frontal seulement dans certaines circonstances, notamment lorsque l'extraction des traces mnésiques requiert des processus actifs de désambiguïsation (Petrides, 2002, 2005), a été examinée (Étude 3). Une tâche de récupération mnésique du contexte dans laquelle la stabilité avec laquelle des items (mots) et des contextes (fonds d'écran colorés) entraient en relations les uns avec les autres était manipulée afin de recruter des processus de désambiguïsation a été administrée. Les patients avec des lésions au cortex frontal dorsomédial gauche présentaient des déficits lors de la récupération mnésique du contexte alors que le cortex préfrontal ventrolatéral droit a été démontré comme étant une région critique pour la récupération mnésique active nécessaire à la désambiguïsation des contextes uniquement lorsqu'ils entrent en relations multiples et instables les uns avec les autres.

En conclusion, la précision des lésions et l'inclusion de groupes témoins ont permis de démontrer qu'aucun déficit généralisé des fonctions exécutives ne résulte de lésions limitées au cortex frontal, mais que des régions précises du cortex frontal contribuent de façon spécifique à des processus cognitifs particuliers.

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Preface

Statement of Original Contributions

In this thesis, I present three studies that make original contributions to the understanding of functions of the frontal cortex. We tested two general issues and three specific hypotheses about prefrontal cortex functions by examining patients with well-documented lesions restricted to the frontal cortex and comparing them with two appropriate control groups, namely patients with lesions to another part of the brain and healthy neurologically intact individuals. This approach provides information whether a brain region is critical for a specific aspect of cognitive processing in humans (e.g., Teuber, 1955; Stuss & Alexander, 2007).

Study 1 addressed the issue of the Frontal Assessment Battery (Dubois et al., 2000). This test battery, as the name indicates, is expected to be sensitive to frontal cortical dysfunction although it has never been validated on a population of patients with lesions restricted to the frontal cortex. This battery is commonly used to assess the level of frontal dysfunctions in different populations, but had been developed with patients with various neurodegenerative diseases who have widespread damage, that is damage to many different parts of the brain in addition to the frontal cortex. Study 1 demonstrated that the global performance score on this battery, as well as that of five of its six subtests, are not sensitive to damage restricted to the frontal cortex. We showed, however, that the verbal fluency (mental flexibility) subtest is sensitive to damage to the left frontal cortex, especially its dorsomedial region, which corroborates previous findings (Stuss et al., 1998; Robinson et al., 2012). Furthermore, by means of rigorous documentation and anatomical analysis of the lesions of the patients showing

verbal fluency impairments, we were able to define more precisely the region that is critical for verbal fluency compared with what was available in the literature. The critical region comprises the supplementary speech zone, the cingulate motor region, the paracingulate cortex and the medial extents of prefrontal areas 8 and 9.

Study 2 addressed the issue of utilization behaviour. In a widely quoted article by Lhermitte (1983), it was argued that frontal damage could result in the demonstration of utilization behaviour, which was defined as the urge of a patient to grasp and use an object that is presented to him without the instruction to do so. Study 2 is the third group study on utilization behaviour, but the first one to select patients with lesions relatively circumscribed to the frontal cortex and to compare their performance with that of well-matched patient and normal control subjects. The two previous studies (De Renzi et al., 1996; Besnard et al., 2009) examined utilization behaviour in patients with diffuse damage to the anterior part of the brain, including to subcortical structures, and did not include brain-lesion and normal control groups. It was not possible to draw specific anatomo-functional conclusions from these studies. In contrast, Study 2 looked at the specific effects of frontal cortex lesions on utilization behaviour. The results demonstrate that neither utilization behaviour nor mere touching of the presented objects is phenomena associated with damage to the frontal cortex: they were observed with the same incidence in the frontal, temporal and healthy control groups. Thus, Study 2 is a well-controlled study that provides for the first time clear negative evidence about the common belief that utilization behaviour is caused by frontal damage.

In Study 3, we provide for the first time clear evidence that the ventrolateral prefrontal cortex is critical for context retrieval when stimuli are linked with multiple contexts in unstable and constantly varying manner and thus memory traces require disambiguation. In contrast, we found that this region is not critical when the stimuli are related to contexts in unique and unambiguous ways. This hypothesis had received support from functional neuroimaging studies (Cadoret et al., 2001; Kostopoulos et al., 2007; Kostopoulos & Petrides, 2003, 2008), but was never confirmed with loss-of-function studies. As is well known, functional neuroimaging evidence is correlative and only lesion studies can establish a causal relation and provide unambiguous evidence with regard to the necessary role of a part of the brain in particular aspects of cognitive processing (e.g., Fellows & Farah, 2005). In addition, this study was the first to demonstrate a direct contribution of the dorsomedial frontal region in context retrieval, regardless of the ambiguity of the relationships between items and contexts in memory. Finally, findings of Study 3 confirmed the well-established fact that structures in the temporal lobe are critical for basic memory recognition (Scoville & Milner, 1957; Smith & Milner, 1981, 1989; Nadel & Moscovitch, 2001; Eichenbaum et al., 2007), unlike the frontal cortex.

Contribution of Authors

The three studies presented in this thesis were co-authored by myself and Michael Petrides. The questions, rationale and methodology were developed by the two of us. I set up all aspects of the tasks described in Study 2 and Study 3. I recruited the patients and healthy control participants, collected and analyzed the data, as well as drafted and revised the manuscripts. Michael Petrides contributed to the detailed analysis of the patients' lesions, to the statistical analyses and to the interpretation of the data. He provided detailed scientific and editorial comments to the various versions of the manuscripts and contributed to the fine-tuning of their final versions.

Study 1 was published in *Brain* in 2013 (Chapados & Petrides, 2013) and study 2 is in press at *Neuropsychologia*. Study 3 has been submitted for publication.

General Introduction

Many general claims have been made about the functions of the 'frontal lobe' (see Stuss & Knight, 2013), such as its involvement in various higher-order cognitive processes that are often grouped together under the term 'executive functions'. The majority of the claims about functions of the frontal lobe have been based on lesion studies in human patients with various aetiologies often presenting extensive injuries to the anterior part of the brain, including the frontal cortex, but also invading other parts of the brain, such as anterior deep subcortical structures (e.g., basal ganglia, thalamus), major white matter tracts and even anterior portions of the parietal and temporal lobes. Such massive damage results in global dysfunction, often referred to as the dys-executive syndrome. However, it is not clear how much of the impairment is due to prefrontal cortical damage per se and how much is the result of subcortical damage (e.g., caudate nucleus) or widespread disruption of hemispheric function and it is impossible to draw precise correlates between prefrontal cortical areas and function from such cases. In addition, often no patient control data are available in such studies.

Nonhuman primate studies with extremely precise lesions restricted to the cortex allow for specific anatomo-functional correlations (e.g., Bachevalier & Mishkin, 1986; Petrides, 1995, 2002, 2005). Although it is impossible to conduct patient studies with the same level of precision and potential for replication, lesion studies in patients with strict inclusion criteria regarding the location and extent of the brain damage and with carefully matched patient controls would come closer to this goal than many patient lesion studies now available in the literature.

Also, the large frontal cortex is very heterogeneous in terms of both structure (e.g., Petrides & Pandya, 1994, 1999, 2002) and function (e.g., Bachevalier & Mishkin, 1986; Petrides, 1995, 2000a, 2005). Each cortical area has distinct cyto- and myelo-architecture, where the composition of neuronal cell bodies and axons and their organization into layers is unique (e.g. Brodmann, 1908). The description of several of these frontal regions will be provided in the literature review. Therefore, any statement about general functions of the prefrontal cortex is likely to lack specificity and leaves the question of how the different prefrontal areas contribute uniquely to distinct executive processes unanswered.

Because of its high spatial resolution, functional neuroimaging offers the opportunity for greater specificity. However, only correlational, and not causal, relationships are possible with this type of methodology. That is, one can say that a specific region is *involved in* a particular function because there is increased activity in this region during a specific task, but one cannot establish that this area is *critical to* the function (e.g., Fellows & Farah, 2005). Only studies showing dysfunction following disruption of an area can provide this anatomo-functional causal link. Therefore, lesion studies with carefully selected neurosurgical patients who underwent circumscribed cortical excisions that are well documented would allow for both causal inferences and relative functional specificity.

The general purpose of this research program was to examine the effect of damage limited to the prefrontal cortex, and no more than the immediately underlying white matter, on functions commonly claimed to be associated with the frontal cortex and to compare it with the effect of damage to another part of

the brain, the temporal lobe. The characteristics of the patients included in this project are presented in the Appendix. Three studies comprise the present thesis. The first study examined whether lesions limited to the frontal cortex cause generalized impairments on a specific battery of tests, the Frontal Assessment Battery (FAB; Dubois, Slachevsky, Litvan & Pillon, 2000) which is thought to be a sensitive measure of frontal function, yet has never been tested on patients with clearly localized frontal lesions. The second study explored whether utilization behaviour, defined as the impulse to grasp and use a presented object even though it is not contextually appropriate to use it, which has been claimed to be due to frontal lesions (Lhermitte, 1983) can indeed be observed in patients without extra-frontal damage. In the third study, we investigated circumstances under which the frontal cortex, especially its ventrolateral and dorsomedial regions, might contribute to mnemonic context retrieval.

General Literature Review

The following review summarizes the findings and issues in the literature about frontal functions that have motivated and influenced us to conduct this research. First, the anatomy of the frontal cortex, especially the frontal regions relevant to the 'executive' and memory retrieval functions covered in this thesis, will be reviewed. Second, some theories about the role of the frontal cortex in executive functions will be examined, with a focus on the Frontal Assessment Battery and on utilization behaviour. Third, the literature pertaining to the role of the frontal cortex in memory retrieval will be reviewed, especially with regards to context memory and active controlled retrieval. Next, the problems with the inclusion criteria and interpretations of previous studies investigating the Frontal Assessment Battery and utilization behaviour will be reviewed in order to address the issues inherent to claims based on populations with widespread brain abnormalities. Finally, the reasons for using an alternative methodological approach will be mentioned along with the goals of the present thesis.

Anatomy of the frontal cortex

The frontal cortex is a large expanse of the human cerebral cortex that lies superior to the lateral fissure and anterior to the central sulcus all the way to the frontal pole. The gyrus immediately anterior to the central sulcus, the precentral gyrus, comprises the motor and premotor cortex. The large cortical region lying in front of it is commonly referred to as the 'prefrontal cortex'. Here, the terms 'frontal cortex' and 'prefrontal cortex' will be used interchangeably to refer to the cortex anterior to the precentral gyrus. The frontal cortex is structurally very

heterogeneous and comprises numerous different areas (Fig. 1) that have been divided and mapped on the basis of their distinct cytoarchitecture (e.g., Brodmann, 1909; Economo & Koskinas, 1925; Sarkissov, Filimonoff, Kononowa, Preobraschenskaja & Kukuew, 1955). The cortical areas also differ in terms of their patterns of connectivity with other cortical and subcortical areas (Petrides & Pandya, 1994, 1999, 2002). Not surprisingly, these distinct areas seem to make distinct types of computations and unique functional contributions to cognition (e.g., see Petrides, 2005; Stuss & Alexander, 2007).

On the lateral surface, the frontal cortex can be subdivided into a dorsal part above the inferior frontal sulcus, the dorsolateral prefrontal cortex, and a ventral part, the ventrolateral prefrontal cortex. There is also an anteriormost part, the frontopolar region (area 10) that also extends medially. The dorsolateral prefrontal cortex is comprised of a posterior part (area 8 and rostral area 6) and an anterior part, the mid-dorsolateral prefrontal cortex (areas 46 and 9/46) and the more dorsally located area 9. Each of these areas have distinct cytoarchitetonic features and unique patterns of corticocortical connections. For instance, areas 46 and 9/46 are strongly interconnected with multimodal temporal areas, paralimbic cortical areas and parietal cortical areas (Petrides & Pandya, 1999). The ventrolateral prefrontal cortex can be subdivided into three regions in a posterior-to-anterior axis: the pars opercularis (area 44), the pars triangularis (area 45) and the pars orbitalis (area 47/12) part of which extends onto the immediately adjacent cortex on the orbital surface (Petrides & Pandya, 1994). Areas 45 and 47/12 are together referred to as the mid-ventrolateral prefrontal cortex (Petrides, 1996, 2002). This region maintains strong connections with ventral limbic areas and

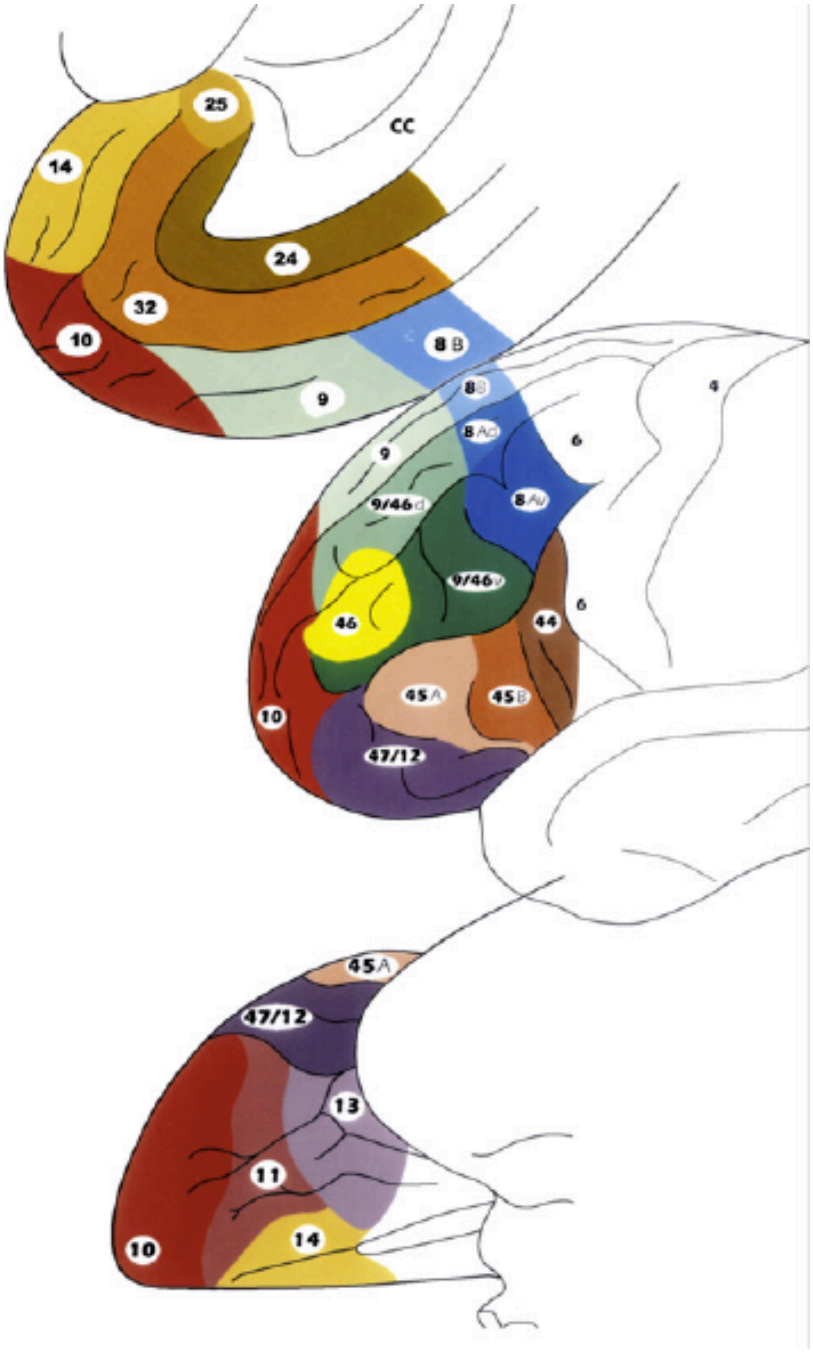

Figure 1. Map of the cortical divisions of the prefrontal cortex as viewed on the medial (top), lateral (middle) and orbital (bottom) surface by Petrides & Pandya (1994).

regions of the lateral temporal cortex (Petrides & Pandya, 2002), suggesting that it can modulate information coming from posterior cortical areas that are involved in different aspects of cognitive processing, especially memory.

On the medial surface of the prefrontal cortex, one can find the cingulate (area 24) and paracingulate (area 32) cortex surrounding the corpus callosum and the subcallosal gyrus (area 25) that lies ventrally. On the medial surface of the superior frontal gyrus, the dorsomedial frontal region comprises the medial extension of areas 6, 8 and 9 and the adjacent ventrally located cingulate region. The supplementary motor complex is the medial extent of the pre-motor cortex (area 6) on the superior frontal gyrus. It lies anterior to the foot representation of the primary motor cortex and superior to the cingulate sulcus. In a caudal-to-rostral axis, it comprises the supplementary motor area, the supplementary eye field and the pre-supplementary motor area (see review by Nachev, Kennard & Husain, 2008). It is interconnected with other structures of the motor system, including the primary motor and cingulate cortex, the basal ganglia, the subthalamic nucleus, the cerebellum and the spinal cord (Jürgens, 1984; Johansen-Berg et al., 2004). Ventral to the supplementary motor complex, motor regions are also found along the cingulate and paracingulate sulci in three distinct human motor clusters (Amiez & Petrides, 2012), which are analogous (Picard & Strick, 1996; 2001) to three well-documented motor areas in the monkey (e.g., Dum & Strick, 1993, 2002). They are interconnected with other motor structures such as the dorsal striatum and the motor and premotor cortex (Beckman, Johansen-Berg & Rushworth, 2009). The dorsomedial frontal cortex is also

strongly linked to the hippocampal/parahippocampal region (Morris, Pandya & Petrides, 1999).

On the basis of this brief review of some frontal cortical areas, one can appreciate their great heterogeneity in terms of their different cytoarchitecture and connectivity with other frontal and nonfrontal areas, implying specific processing in each area.

Frontal cortex and 'executive' functions

The frontal cortex is a very complex region of the brain that is believed to play a central role in cognition (see Stuss & Knight, 2013). Because of its massive interconnections with many parts of the brain (Petrides & Pandya, 1994, 1999, 2002), the frontal cortex appears to be involved in supra-modal, supervisory and integrative high-order cognitive processes that are often labeled as 'executive functions'. Executive functions refer to the initiation and planning of behaviour, decision making, self-regulation, monitoring, energizing, flexibility, and inhibition, which enable human subjects to elaborate and engage successfully in goal-directed and adaptive behaviours (Lezak, 1995; Stuss, 2011).

While some argue that the frontal cortex is the seat of a central undifferentiated executive system (Duncan & Miller, 2002), which has also been described as the general factor *g* or as fluid intelligence (Roca et al., 2010, 2013), the idea of a diversity of discrete executive functions controlled by different prefrontal cortical areas has received strong support in the literature (see Bachevalier & Mishkin, 1986; Petrides, 2005; Stuss & Alexander, 2007; Stuss, 2011). However, because impairments in executive functions have been reported

following damage to the anterior part of the brain, there is a long and tenacious history of equating 'frontal lobe functions' and 'executive functions' as two synonymous terms that can be used interchangeably. This view has greatly influenced the literature and consequently, many measures and behaviours intended to capture and assess general frontal functions have emerged, among them the Frontal Assessment Battery and utilization behaviour.

Frontal Assessment Battery. The Frontal Assessment Battery is a brief tool designed to assess the presence of executive function impairments, assumed to be caused by frontal damage (Dubois et al., 2000). It comprises six subtests: 'conceptualization', 'mental flexibility', 'action programming', 'sensitivity to interference', 'inhibitory control', and 'environmental autonomy'.

'Conceptualization' examines the ability to extract concepts of similarity in a verbal abstraction subtest. 'Mental flexibility' looks at the capacity to retrieve words responding to specific criteria and to maintain this non-automatic production over time during a verbal fluency trial. 'Action programming' assesses the ability to repeat a three-step motor sequence, the Luria's "fist-palm-edge" sequence. 'Sensitivity to interference' examines the capacity to provide the correct response to conflicting instructions, that is, to inhibit the intuitive response and provide the opposite response. 'Inhibitory control' measures the ability to withhold a strong impulsive response in a go-no go paradigm. Finally, 'environmental autonomy' assesses the capacity to inhibit a grasping reflex to stimulation of the palms. These tasks were believed to capture different executive functions mediated by the frontal cortex and to be sensitive to abnormalities occurring in this region of the brain.

Utilization behaviour. Utilization behaviour was first described by Lhermitte (1983) as the automatic grasping and utilization of objects present in the environment, even though it is not contextually appropriate and the patients were not instructed to grasp and use the objects. Lhermitte argued that the presentation of the objects compels the patient to grasp and use them. For example, if a piece of paper and a pencil are presented to patients demonstrating utilization behaviour without instructions, they will pick up the pencil and start writing on the piece of paper.

Utilization behaviour is often observed in association with 'imitation behaviour', which occurs when an individual reproduces the gestures of the examiner without prior instructions to do so (Lhermitte, Pillon & Serdaru, 1986). Another related phenomenon, the environmental dependency syndrome, was put forward by Lhermitte (1986) to explain deficiency in personal control over the whole context, not just a given object. For example, one of his patients would wash the dishes when visiting a kitchen, whereas another would undress and lie on the bed upon entering a bedroom. These three behavioural syndromes have been considered as disturbances of motor behaviour, resulting in motor release phenomena (Archibald, Mateer & Kerns, 2001), that is, the exhibition of behaviours that would normally be withheld.

Lhermitte and his group reported that utilization behaviour was common among patients with bilateral and unilateral lesions to the anterior part of the brain (Lhermitte, 1983; Lhermitte et al., 1986), and thus ascribed it to the frontal lobes. They proposed as a potential mechanism that the frontal lobes exert inhibition and modulation over the environmentally and externally driven utilization behaviours

that are initiated by the parietal cortex. Loss of the frontal inhibition would thus result in utilization behaviour (Branzelli & Spinnler, 1998).

Frontal cortex and memory

Finally, the present thesis (Study 3) also examines how the frontal cortex contributes to memory. In contrast to the well-established fact that medial temporal lobe structures, especially the hippocampus, entorhinal and parahippocampal cortex, are critical for memory (Scoville & Milner, 1957; Smith & Milner, 1981, 1989; Nadel & Moscovitch, 2001; Eichenbaum, Yonelinas & Ranganath, 2007), the functional contribution of the frontal cortex is still debated. Some parts of the frontal cortex, such as the caudal orbital and the caudal medial regions including the septal area, might have a somewhat direct role in memory formation because of their close relationship with the medial temporal lobe, in terms of both their strong interconnections and shared similarities in cytoarchitecture. However, it is not clear whether the lateral part of the frontal cortex is also critical in memory, or if it rather plays a secondary role (Petrides, 1994; Petrides, 2000a; Miyashita, 2004).

An episode in memory consists of both the event itself and the context surrounding this event, such as when and where it happened (Tulving, 1972; 1983). Greater activation of the frontal cortex during retrieval of the context than of the event itself has been demonstrated in various functional neuroimaging and electrophysiological studies (e.g., Dobbins, Foley, Schacter & Wagner, 2002; Fujii at al., 2004; review by Mitchell & Johnson, 2009). In addition, there is evidence from lesion studies that patients with frontal damage are impaired in

source memory, which can be considered as a form of context retrieval, despite intact fact memory (e.g., Shimamura & Squire, 1987; Janowsky, Shimamura & Squire, 1989; Shimamura, Janowsky & Squire, 1990; Schacter, 1995; Duarte, Ranganath & Knight, 2005). Source memory refers to memory for the context in which an event was experienced and how the information was acquired (Johnson, Hashtroudi & Lindsay, 1993; Mitchell & Johnson, 2009).

However, studies of patients with lesions *limited* to the prefrontal cortex did not observe impairments in source memory. One study showed that patients with lesions to the frontal cortex were not specifically impaired in the recall of factual information and its source compared with control participants and patients with temporal lobe lesions (Thaiss & Petrides, 2003). This study examined two aspects of the context surrounding the memory: identity (who provided the fact) and temporal source memory. Another study reported similar results for the recall of autobiographical memories and their context (Thaiss & Petrides, 2008). Patients with prefrontal cortex lesions were not impaired in recalling details and temporal context of recent autobiographical events. However, they were less likely to use spontaneously organizational strategies to help retrieval, such as temporally ordering the events. One might wonder why patients with frontal lesions perform well on source memory in some studies but not others. In other words, is there a part of the prefrontal cortex that might be necessary for context retrieval and under what circumstances?

It has been argued that parts of the prefrontal cortex, especially the dorsolateral and ventrolateral regions, play an indirect role in memory such as the application of various control processes required for memory in particular

situations (Petrides, 2000a, 2002, 2005; Moscovitch, 1992; Stuss & Alexander, 2005; Badre & Wagner, 2007). For instance, it has been shown that lateral prefrontal cortex lesions impair the monitoring of information in working memory (Petrides & Milner, 1982) and studies with macaque monkeys have shown that the mid-dorsolateral prefrontal cortex (areas 46 and 9/46) is a specialized region for the on-line monitoring of multiple pieces of information in working memory (Petrides 1991, 2000b). Activation in this region (areas 46 and 9/46) was dissociated from activity in the mid-ventrolateral prefrontal cortex (areas 45 and 47/12) in several studies (Petrides, 1996). In an attempt to explain why lateral frontal cortical lesions do not cause amnesia, Petrides (2002, 2005) made the distinction between automatic and active memory retrieval processing. Memory retrieval is more or less automatic when strong and stable relationships exist between stimuli in memory and when the presence of one piece of information (a stimulus) will automatically trigger the stored representations of the memory of that stimulus and other stimuli/contexts that are strongly associated with that stimulus (Petrides, 2002; 2005). Automatic retrieval can be either stimulus- or context-driven. On the one hand, when a strong stimulus-stimulus association exists, one cue will automatically trigger retrieval from memory of information that is strongly related to the cue. For example, if one is presented with the word Levi's, one will automatically think of blue jeans. On the other hand, consistent with the model proposed by Johnson and colleagues (1993), this is also true for strong stimulus-context associations. Strong and stable relations can exist between a stimulus and an event or a context when the association is constantly repeated (e.g. person A sees person B every time she goes to the gym) or when this

association is unique (e.g. person A met person B only once when person A went to Paris). The mere presentation of person B to person A will trigger the stored representations of the event (training/trip) and the context (gym/Paris). In this case, the stimulus and the retrieved information have strong, stable and unique preexisting relations to one another, which were not weakened by interference due to associations with other pieces of information. In contrast, active memory retrieval is required when automatic processes are not sufficient for successful memory retrieval, that is, when stimuli in memory are related to one another in an unstable or ambiguous fashion (Petrides, 2002). It would then require effortful, controlled processing and the use of strategies for retrieving a piece of information from memory. Such strategies include the active selection and the judgment of the retrieval product and its relevance with the goal (Petrides, 2002). The retrieved memory is either judged satisfactory and the process stops, or it is rejected and the process is reinitiated until successful retrieval is achieved.

Petrides (2002; 2005) argued that the mid-ventrolateral prefrontal cortex might be a critical part of the prefrontal cortex for the active controlled retrieval of information in situations where various pieces of information exist in multiple associations with one another. Under these circumstances, automatic processes are not sufficient for successful memory retrieval and, therefore, top-down control processing is necessary to disambiguate the memory traces that are assumed to lie in the posterior association neocortex. Neuroimaging studies aimed at testing this hypothesis have provided evidence in support of this hypothesis in the sense that activity increased in the mid-ventrolateral prefrontal cortex during retrieval of different stimulus features that occurred in association with each other in a

random and equiprobable way (Cadoret, Pike & Petrides, 2001; Kostopoulos, Albanese & Petrides, 2007; Kostopoulos & Petrides, 2003, 2008).

In such situations, the ventrolateral prefrontal cortex may be recruited to exert top-down control on posterior cortical regions in order to isolate particular pieces of information and the specific information associated with or embedded in them, but not for the retrieval of information associated in a stable and unambiguous fashion. The increased activation in the mid-ventrolateral prefrontal cortex related to active mnemonic retrieval was found regardless of the stimulus material (visual, verbal, auditory and tactile) and of the manipulated stimulus features. Thus, one could hypothesize that the ventrolateral prefrontal cortex is also recruited for context retrieval when active strategic processes are required to disentangle item and context pieces of information that are associated in an unstable fashion or in multiple relationships with one another, but not when contextual information is associated with the event in a unique and stable way. Even though functional neuroimaging studies clearly show the involvement of the mid-ventrolateral prefrontal cortex in mnemonic retrieval when stimuli are linked to different contexts in multiple ways (Cadoret et al., 2001; Kostopoulos et al., 2007; Kostopoulos & Petrides 2003; 2008), only a lesion study in humans would confirm the essential contribution of the prefrontal cortex, and more specifically the ventrolateral prefrontal region, in such memory retrieval processes.

Issues with original lesion studies

The majority of the original findings about frontal cortex functions have been based on lesion studies in humans. One issue with many human lesion

studies of the frontal cortex is the rather loose definition of what constitutes a frontal lesion, leading to the inclusion of many cases with extra-frontal damage.

While some findings about the frontal cortex are based on circumscribed surgical excisions (e.g., Milner, 1982), many other studies have examined patients with neurodegenerative diseases (e.g., Dubois et al., 2000; Roca et al., 2013), cerebrovascular accidents (e.g., Lhermitte, 1983), or traumatic brain injury (e.g., Luria, 1969). In addition to the considerable variability in the nature of the lesions in the studied patient populations making them difficult to compare, the massive injuries resulting from those aetiologies included the frontal cortex, but often also invaded other parts of the brain, such as subcortical structures and fibre tracts lying in the depth of the frontal lobes. Other cortical areas outside the prefrontal cortex, such as anterior parietal and temporal cortical areas, were also often affected. While the findings obtained with these populations have practical value regarding the effects of these conditions on behaviours, they do not allow for specific inferences about the functions of the frontal cortex. In other words, because many brain areas are affected, resulting in impairments of several cognitive functions, it is impossible to ascribe a particular impairment to the effect of a lesion in a particular cortical area. The following two sections describe the patient populations: 1) studied to develop the Frontal Assessment Battery, and 2) in which utilization behaviour was first reported and later observed; and how their inclusion criteria might be problematic to draw specific conclusions.

Patients studied for the development of the Frontal Assessment Battery (FAB). The FAB was developed by Dubois and colleagues (2000) who examined performance of patients with different neurological conditions and

compared it with healthy control participants. The neurological conditions examined, namely Parkinson's disease, multiple system atrophy, corticobasal degeneration, progressive supranuclear palsy, and frontotemporal dementia, were selected based on the assumption that they cause damage to the frontal part of the brain. However, a brief review of the current literature on the anatomical distribution of the pathological findings clearly shows that none of these neurodegenerative conditions cause dysfunction that is *limited to* the frontal cortex; the pathological findings appear in widespread cortical and subcortical damage.

Parkinson's disease. Out of 121 patients studied by Dubois et al. (2000), 24 suffered from Parkinson's disease. It is primarily a movement disorder affecting the dopaminergic pathway connecting the substantia nigra with the basal ganglia, but it also involves several other structures in the central and peripheral nervous systems (Jellinger, 2011). The pathology follows a predictable progression from the brainstem and the olfactory system to the medial temporal lobe, involving the amygdala, the hippocampus and the entorhinal cortex, and later to prefrontal areas, high-order association areas of the parietal, temporal and occipital lobes, and eventually also in premotor and first-order sensory association areas (Braak et al., 2003; Braak, Ghebremedhin, Rub, Bratzke & Del Tredici, 2004). Thus, many brain regions are affected in Parkinson's disease before the prefrontal cortex is involved, and damage to the downstream subcortical and medial temporal lobe areas is potentially more extensive and important (Braak et al., 2004). Even though the prefrontal cortex was probably damaged in the patients with Parkinson's disease studied by Dubois et al. (2000), it is not possible

to assume that their impairments reflect primarily dysfunction of the frontal cortex.

Multiple system atrophy. Six patients studied by Dubois and colleagues suffered from another neurodegenerative disease, multiple system atrophy. This condition is characterized by widespread degeneration of the central nervous system, particularly of the nigrostriatal system, leading to heterogeneous clinical presentations including autonomic failure, parkinsonism, cereballar ataxia and corticospinal tract dysfunctions (Gilman et al., 2008). The pathology is characterized by glial cytoplasmic inclusions and cell loss in various structures of the spinal cord, brainstem, basal ganglia, major projection fiber tracts (internal and external capsules), olfactory bulbs and cerebellar white matter (Wakabayashi & Takahashi, 2006; Wenning, Stefaniva, Jellinger, Poewe & Schlossmacher, 2008). At the cortical level, abnormalities have been observed mostly in motor cortical areas (e.g. precentral gyrus) and the posterior part of the lateral prefrontal cortex, the anterior portion of the paracentral lobule and the cingulate sulcus (Papp & Lantos, 1994). In other words, the affected frontal cortical areas in multiple system atrophy are posterior frontal areas generally involved in motor functions. In conclusion, there is no doubt that patients with multiple system atrophy have abnormalities widely distributed in the central nervous system, especially in the brainstem and subcortical structures, extending far beyond the frontal cortex.

Corticobasal degeneration. This rare neurodegenerative pathology involves, bilaterally, the superior paracentral region of the brain, including the supplementary motor area, the lateral part of the posterior frontal cortex and the

anterior parietal cortex, as well as the subjacent white matter (Lee et al., 2011). Subcortical structures, such as the basal ganglia, substantia nigra and thalamus, and some important fiber tracts, such as the corpus callosum and internal capsule, are also damaged (Lee et al., 2011). Clearly, it is not solely the frontal cortex that is affected in this disease. In addition, this condition is very rare and many syndromes with similar clinical manifestations, but different pathological substrates (e.g. Alzheimer's disease, progressive supranuclear palsy and frontotemporal lobar degeneration) may be mistakenly diagnosed as corticobasal degeneration (Ling et al., 2010). The 21 patients considered as having corticobasal degeneration in the study of Dubois et al. (2000) did not have pathological confirmation of the disease, so they could have presented any corticobasal syndrome without the pathology described above.

Progressive supranuclear palsy. Forty-seven patients presented with progressive supranuclear palsy. In this neurodegenerative condition, the anatomical distribution of the pathology in the central nervous system is heterogeneous; and one typical presentation as well as different atypical presentations are recognized (Dickson, Rademakers & Hutton, 2007; Dickson, Ahmed, Algom, Tsuboi & Josephs, 2010). In the first description of the typical form of progressive supranuclear palsy, Steele, Richardson and Olszewski (1964) identified pathological changes in the globus pallidus, in several brain stem nuclei and in parts of the cerebellum, but only occasionally in the cerebral cortex. The precentral gyrus seems to be the most affected cortical area (Dickson et al., 2010). An atypical form of the disease with frontal lobe dementia is associated with cortical synapse loss in the temporal, parietal and motor cortex, in addition to the

prefrontal cortex (Bigio et al., 2001). Since no details were provided regarding the cognitive symptomatology or neuropathology of the progressive supranuclear palsy patients investigated in the initial study (Dubois et al., 2000), we do not know if the prefrontal cortex of these patients was affected by the pathology.

Frontotemporal dementia. Finally, 23 patients studied by Dubois were diagnosed with frontotemporal dementia. This is a broad term encompassing a large spectrum of dementias of the non-Alzheimer type and generally characterized by frontotemporal lobar degeneration (Pan et al., 2012). It is clinically, pathologically and anatomically heterogeneous, and three subtypes have been described: one behavioural variant and two language variants, i.e. semantic dementia and nonfluent progressive aphasia (Seltman & Matthews, 2012). The behavioural variant is predominantly associated with cortical atrophy in both medial and lateral prefrontal areas, including the anterior medial frontal and cingulate cortex, the frontopolar region and the middle and superior frontal gyri (Pan et al., 2012). However, atrophy is also detected in the insular cortex and in subcortical grey matter areas, such as the basal ganglia and thalamus (Chow et al., 2008), as well as in the temporal and parietal lobes (Whitwell et al., 2009). The semantic dementia variant is mostly associated with atrophy in the anterior temporal lobe, posterior insula and medial frontal regions (Rosen et al., 2002; Gorno-Tempini et al., 2004), whereas nonfluent progressive aphasia cases show atrophy in the left inferior frontal gyrus, inferior precentral sulcus and gyrus, middle frontal gyrus and anterior part of the insula (Gorno-Tempini et al., 2004). Atrophy in caudate nucleus and other subcortical structures has also been demonstrated in both language variants (Gorno-Tempini et al., 2004; Chow et al.,

2008). In their study, Dubois and colleagues (2000) did not specify the type of frontotemporal dementia sustained by their patients, but from their mention of a progressive onset of behavioural changes as an inclusion criterion, they might have included mostly patients with the behavioural variant. It is possible that brain dysfunction in these patients was mainly concentrated in the frontal lobes, but it was certainly not restricted to the frontal cortex.

It is clear from this brief review that, although frontal cortical pathology may have been involved in many of the cases studied by Dubois et al. (2000), there must have been widespread extra-frontal abnormality in these cases on which the Frontal Assessment Battery was validated. There is also a great variability in the anatomical distribution of the pathology not only across the five diseases, but also within each disease. This fact raises the question of whether the impairments observed in these patients and ascribed to the frontal cortex were actually caused primarily by the frontal dysfunctions, or rather by the widespread brain damage, including the frontal cortex.

Patients studied for utilization behaviour. Lhermitte (1983) first observed utilization behaviour in patients who sustained massive damage to the anterior part of the brain caused by different neurological conditions, including glioma, aneurysms and Alzheimer's disease. The anatomical examination of five cases of utilization behaviour was carried out: Case 1 had a large aneurysm in the inferior orbital aspect of the right frontal lobe with cortical and subcortical damage including the caudate nucleus and the corpus callosum; Case 2 had a left frontal arteriovenous malformation in the premotor area and in the posterior part of the middle frontal gyrus and Broca's gyrus, extending in the subjacent

subcortical region; Case 3 had sustained a massive tumour excision around the third ventricle, clearly involving significant subcortical damage, mostly the right caudate nucleus, and projection fibers; Case 4 had extensive right hemispheric damage encompassing the frontal, parietal and temporal lobes as well as the caudate nucleus in the subcortical region, according to the computed tomography scan; and Case 5 had a large glioblastoma extending throughout the whole right frontal lobe including both cortical and subcortical regions. On the basis of these cases, Lhermitte attempted to ascribe utilization behaviour to particular parts of the frontal cortex. He suggested that the orbital cortical surface was the most likely region to be involved in utilization behaviour, but he concluded that he could not clearly identify the critical frontal regions. He also raised the issue of the potential role of subcortical structures, such as the caudate nucleus. It is clear that none of these cases studied can prove that utilization behaviour is the result of damage restricted to the frontal cortex.

In the next report of utilization behaviour, Lhermitte and colleagues (1986) tested the presence of the behaviour in more patients with lesions in the frontal region of the brain. The anatomical location of the lesions was not documented for individual patients, but an overlapping of the lesions of patients with utilization behaviour pointed to involvement of the inferior half and the mediobasal area of the frontal lobes, including subcortical structures, including the internal capsule and the anterior part of the basal ganglia. In addition, utilization behaviour was found in two patients with focal damage to deep structures involving the thalamus, the internal capsule and the caudate nucleus, in 10 patients with Alzheimer's disease and in a few patients with other diffuse

neurological conditions, such as Parkinson's disease, progressive supranuclear palsy, normal pressure hydrocephalus and other nonspecified disorders. In conclusion, the population of patients on which the claim that damage to the frontal cortex is the reason for utilization behaviour was based does not permit such a conclusion.

To the best of our knowledge, only two additional group studies on utilization behaviour have been published. One study comparing patients with relatively focal frontal damage with patients with non-frontal brain lesions observed utilization behaviour in only two out of 52 frontal patients (De Renzi, Cavalleri & Facchini, 1996). One had suffered an infarct in the region of the cingulate gyrus and the other had a lesion on the medial and lateral aspects of the frontal lobes also affecting the subventricular zone, again two patients that are problematic with regard to the claim that frontal cortical damage results in utilization behaviour. The other group study demonstrated utilization behaviour in six patients assumed to have damage in the frontal lobes, but whose lesions were reported to result from frontotemporal dementia in two cases, and to extend outside the frontal lobes in the other four cases involving significantly subcortical structures or other cortical and subcortical structures (Besnard et al., 2009). The authors could not ascribe utilization behaviour to the frontal cortex given the extensive cortico-subcortical damage in these patients.

In addition, various single case reports of utilization behaviour have been published. They pointed to involvement of different areas of the prefrontal cortex, deep structures within the frontal lobes, or cortico-cortical and cortico-subcortical connections as being responsible for the release of utilization behaviours.

Shallice, Burgess, Schon and Baxter (1989) observed utilization behaviour in a patient with bilateral inferior medial frontal lesion that extended posteriorly and subcortically, invading the rostrum of the corpus callosum, the internal capsule bilaterally and the right head of the caudate nucleus and putamen. In other single case studies, the dorsomedial frontal cortex, including the supplementary motor area (SMA) and the cingulate cortex, were often involved, either unilaterally (Boccardi, Della Sala, Motto & Spinnler, 2002) or bilaterally (Fukui, Hasegawa, Sugita & Tsukagoshi, 1993; Brazzelli, Colombo, Della Sala & Spinnler, 1994), in combination with damage to underlying fiber tracts (Laplane, Degos, Baulac & Gray, 1981; Ishihara, Nishino, Maki, Kawamura & Murayama, 2002) and the head of the caudate nucleus (Degos, da Fonseca, Gray & Cesaro, 1993), or in combination with damage to the temporal cortex (Assal, 1985). Utilization behaviour was also observed in a case of bilateral damage to the medial frontal and temporal lobes (Balani, Soto & Humphreys, 2009). Other single case studies reported utilization behaviour without damage to the frontal cortex, but with damage to subcortical structures lying deeper in the frontal lobe and interconnected with the frontal cortex, such as the paramedian thalamic region, bilaterally (Eslinger, Warner, Grattan & Easton, 1995), the right ventroanterior and intralaminar nuclei of the thalamus (Hashimoto, Yoshida & Tanaka, 1995), and the right caudate nucleus (Rudd et al., 1998).

It is clear from the above review that the frontal cortical damage was always accompanied by widespread extra-frontal cortical and subcortical damage in the patients exhibiting utilization behaviour. The claim, therefore, that utilization behaviour is a specific impairment that can be ascribed solely to frontal

dysfunction cannot be supported and raises the question of whether utilization behaviour can result from lesions limited to the frontal cortex, i.e. damage that does not extend to extra-frontal cortical or subcortical damage.

The above examination of the pathology and lesions sustained by patients in previous studies of 'frontal' functions demonstrates that many structures were damaged in addition to the frontal cortex. In patients with various neurodegenerative diseases (e.g., Dubois et al., 2000) and large damage due to other etiologies (e.g., Lhermitte, 1983), abnormalities and removals also included extra-frontal cortical areas, such as the medial temporal lobe and the parietal cortex, subcortical structures, such as the basal ganglia, the thalamus and brainstem nuclei, and even the cerebellum and spinal cord in some cases. In addition, important white matter fiber tracts lying under the frontal cortex might have been damaged, thus disconnecting inputs and outputs of the overlying cortical area but also of other areas. For instance, the often-damaged internal capsule (e.g., Lhermitte, 1983; Shallice et al., 1989) contains the corticospinal tract and projection fibers connecting almost the entire cortex with subcortical structures, such as the thalamus and the brainstem. Therefore, in addition to damaging the connections between the frontal cortex and other structures, it may also disconnect other cortical regions from their inputs and outputs, thus preventing these regions to function normally. Commissural fibers of the rostral portion of the corpus callosum can also be cut by damage to the anterior part of the brain, leading to disconnection of corresponding cortical areas between the two hemispheres. Lesions to the rostrum, genu and anterior part of the body of

the corpus callosum disconnect fibers from orbitofrontal, lateral prefrontal and motor areas, respectively.

Finally, even when the damage is restricted to the frontal cortex, because it is heterogeneous, it is likely to include many different areas, thus affecting many distinct cognitive processes (e.g., Bachevalier & Mishkin, 1986; Petrides, 1995, 2000a, 2005). In order to isolate specific cognitive processes (e.g., active memory retrieval processes), one needs precise lesions circumscribed to one, or very few, areas (e.g., ventrolateral prefrontal areas 45 and 47/12). In addition, in order to draw specific conclusion about a specific area (e.g., area 45), the excision must only damage the immediately subjacent white matter, comprising the connections to and from this area. However, if the lesion is deeper and damages the fibers that are traveling under area 45 and going, for instance, to area 46 just dorsal to it, then the observed impairment may be caused by the disconnection of area 46, but not by the damage to area 45.

Proposed alternative approach and goals of the present research

One ideal way to examine the question whether frontal cortical damage actually causes the claimed impairments would be to examine neurosurgical patients with the precise excision of a single frontal cortical area (e.g., the mid-ventrolateral prefrontal area 45) without any underlying white matter damage in order to allow the communication between other frontal areas, or between frontal areas and other brain regions. One would then compare the effect of such lesion with that resulting from control excisions of another frontal cortical area (e.g., the mid-dorsolateral area 9/46) and of a non-frontal cortical area (e.g.,

parahippocampal cortex). Only with this approach, one can demonstrate that impairment on function X is specific to the frontal cortical area A, but dissociated from frontal cortical area B, non-frontal cortical area C or communication pathways between other cortical areas, traveling under the removed area A (e.g., Teuber, 1955; Stuss et al., 2005; Stuss & Alexander, 2007). This level of precision and control can be achieved only in animal studies, such as studies in nonhuman primates and in rodents (e.g., Bachevalier & Mishkin, 1986; Petrides, 1995; Abela & Chudasama, 2013), but not in human studies. Only animal research allows one to create serial identical lesions that perfectly isolate a specific region of interest.

However, in contrast to previous patient studies with extensive and poorly defined lesions to the anterior part of the brain in which no precise anatomo-functional correlations are possible, the use of neurosurgical tumour or epilepsy patients with well-documented excisions approaches the precision of animal lesion studies. With human subjects, we must insist on the highest level of precision possible by carefully documenting the lesions and setting rigorous inclusion criteria of the patients to be studied. A control group of patients with brain damage must also be studied to rule out the non-specific effects of brain damage (Teuber, 1955). These criteria were not followed in previous studies in which the pathology was not documented and patient control groups were not included as a comparison (e.g., Lhermitte, 1983; Dubois et al., 2000; Besnard et al., 2009).

In the studies reported in the present thesis, the location of lesions was documented by means of post-operative Magnetic Resonance Imaging (MRI)

scans or tracings of the excisions by neurosurgeons or neurologists. First, patients with evidence of damage extending outside the prefrontal cortex, such as damage to subcortical structures (e.g., basal ganglia) and/or non-frontal posterior cortical areas, were excluded. Thus, any impairment observed in the present studies could be attributed to damage of the frontal cortex. This, however, cannot be guaranteed in studies not documenting the patients' lesions, using clinical considerations to determine the location and extent of lesions, including patients with neurological conditions known to cause widespread damage to the central nervous system, or grouping patients with heterogeneous etiologies and lesions that are difficult to compare (e.g., Anderson, Damasio & Tranel, 1990). Second, given the anatomical heterogeneity of the prefrontal cortex both in terms of cytoarchitecture and connections (e.g., Petrides & Pandya, 1994, 1999, 2002), the specification of precise lesion location allows us to determine whether a particular prefrontal cortical region, such as the ventrolateral and dorsomedial prefrontal regions, contributes to particular aspects of cognitive function, and not just to make general statements about the frontal cortex.

In addition to the strict anatomical inclusion criteria, we excluded patients with impaired general functioning as measured by IQ lower than 79, patients with psychiatric disorders, or undergoing radiotherapy or chemotherapy treatments at the time of testing (Taphoorn & Klein, 2004). In addition, because cognitive functioning might have been affected by more generalized and diffuse effects of disease and treatments (e.g., general anesthesia, mood disturbances and antiepileptic or corticosteroid medication), we included a patient control group with temporal lobe lesions due to the same etiologies. Therefore, the functional

impairments observed in the present patients more likely reflect the effects of the lesions to the specific cortical regions, rather than any other general factor related to brain damage. The large number of patients with such clean lesions also permitted for more robust and clear findings.

In the first study, the performance of patients with damage restricted to the frontal cortex on the Frontal Assessment Battery, a commonly used tool intended to measure frontal dysfunction, was assessed. The second study examined whether such lesions result in utilization behaviour. Because the above generalized impairments were originally observed in patients with widespread and poorly defined brain lesions extending far beyond the frontal cortex, it was necessary to examine whether these impairments could indeed be ascribed to lesions *restricted* to the frontal cortex in comparison with patients with temporal lobe lesions and healthy control participants.

Finally, in Study 3, the hypothesis that the ventrolateral region of the frontal cortex is critical to context retrieval when multiple stimuli-to-context relationships exist was tested. We examined performance of patients with lesions restricted to the frontal cortex on three memory retrieval conditions in which the stability of the relationships between stimuli (words) and the contexts in which they occurred (backgrounds) was manipulated (Kostopoulos & Petrides, 2003; 2008). In a control condition, the *recognition memory condition*, only basic recognition memory was required to differentiate a series of previously presented words-on-backgrounds from new words on new backgrounds. In the two experimental conditions, retrieval of the specific context was required, but the stability of the association between words and backgrounds varied. In the *stable*

context retrieval condition, each word was presented on only one background (establishing a unique relationship) and subjects had to retrieve the specific background on which each word was presented. In contrast, the relationships between words and backgrounds in the *unstable context retrieval condition* were unstable in the sense that all words had appeared on all backgrounds across trials and, thus, the subjects had to retrieve the specific background on the particular trial. In this condition, the need to retrieve the specific context in memory from other contexts that were not relevant to the particular trial was maximal.

Performance of patients with prefrontal cortex lesions was contrasted with that of patients with temporal lobe lesions and normal control participants. In addition, in order to test the prediction about the specific contribution of the ventrolateral prefrontal region, the frontal group was divided into 1) patients with lesions including the ventrolateral prefrontal region, 2) patients with lesions including the dorsomedial prefrontal region and 3) patients with frontal lesions sparing both the ventrolateral and dorsomedial frontal regions. Patients with lesions including the ventrolateral prefrontal region were expected to perform normally in context retrieval if items and contexts were linked in a unique and stable relationship (stable context retrieval condition), but to be impaired if items were associated to multiple contexts (unstable context retrieval condition). In the latter condition, top-down control processes emanating from the ventrolateral prefrontal cortical region would be expected to disambiguate memory traces and identify the relevant stimulus-to-context association from other similar, but irrelevant, stimulus-to-context associations.

Study 1

Impairment only on the Fluency Subtest of the Frontal Assessment Battery after Prefrontal Lesions

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Abstract

The Frontal Assessment Battery is a set of six subtests that is widely used to assess frontal cortical executive dysfunction. Performance on the Frontal Assessment Battery has been shown to be sensitive to various neurodegenerative diseases, but it has never been shown to be sensitive to damage restricted to the frontal cortex. Thus, despite its wide use, it has never been validated on an appropriate population of patients with frontal lesions. The present study shows that of the six subtests that comprise the Frontal Assessment Battery, only performance on the verbal fluency subtest (mental flexibility) was specifically sensitive to injury restricted to the frontal cortex. Performance of patients with damage to the dorsal part of the medial frontal region in the language dominant left hemisphere was impaired. None of these patients was aphasic at the time of testing. The critical region in the dorsomedial frontal cortex includes the supplementary speech zone but is not restricted to it: It extends into the cingulate motor region and the paracingulate cortex as well as the medial prefrontal areas 8 and 9. The results indicate that the Frontal Assessment Battery is not a sensitive measure of prefrontal cortical dysfunction, except for the verbal fluency subtest.

Introduction

Many claims have been made about the functions of the prefrontal cortex (see Stuss & Knight, 2013). The prefrontal cortex is not a structurally or functionally homogeneous part of the brain: it comprises many different cytoarchitectonic areas with distinct cellular structure and connectivity patterns and, as expected, there is evidence that these areas make distinct functional contributions (e.g., see Petrides, 2005). Although there is general agreement that the prefrontal cortex is involved in various cognitive processes that are often described as "executive", there is less consensus on how to assess these frontal cortical functions. Over the years, several neuropsychological tests intended to measure aspects of frontal cortical function have been used, such as the Wisconsin Card Sorting Test (Milner, 1963; review by Nyhus & Barcelo, 2009), verbal fluency (Milner, 1964; Benton, 1968) and nonverbal fluency (Jones-Gotman & Milner, 1977) tasks, and the self-ordered pointing task (Petrides & Milner, 1982). In addition, various test batteries, such as the Executive Interview (EXIT-25; Royall, Mahurin & Gray, 1992) and the Frontal Assessment Battery (FAB; Dubois et al., 2000) have been developed.

The FAB was designed as a fast and efficient bedside battery to detect frontal lobe dysfunction in a variety of patients and has been shown to be easy to administer and not frustrating for patients (Moorhouse, Gorman & Rockwood, 2009). The FAB is divided into six subtests, each one assessing an "executive" function thought to be subserved by the frontal cortex: conceptualization, mental flexibility, motor programming, sensitivity to interference, inhibitory control, and environmental autonomy (Dubois et al., 2000).

Dubois and colleagues (2000) compared the performance of healthy control subjects with that of patients having different neurological conditions that involve widespread cortical and subcortical damage, including damage to the frontal cortex. The neurological conditions were Parkinson's disease, multiple system atrophy, corticobasal degeneration, progressive supranuclear palsy, and frontotemporal dementia. Because the patients were significantly impaired on the FAB, the battery has been considered a sensitive test of frontal dysfunction. It should be noted, however, that in none of the patient populations in which the sensitivity of this battery to "frontal" dysfunction was assessed had pathology restricted to the frontal cortex. The patients were suffering from neurodegenerative diseases with widespread cortical and subcortical pathology. Parkinson's disease affects primarily the dopaminergic pathway linking the substantia nigra with the basal ganglia and gradually involves an increasing number of structures, such as the medial temporal lobe, the prefrontal cortex, other cortical association areas and, even, primary sensory and motor areas (Jellinger, 2011). Multiple system atrophy is characterized by widespread central nervous system degeneration, including motor cortical areas, basal ganglia, brainstem, cerebellar and spinal cord structures (Wakabayashi & Takahashi, 2006). Corticobasal degeneration involves, bilaterally, the paracentral region, the supplementary motor area, the lateral prefrontal cortex, the basal ganglia and the thalamus (Lee et al., 2011). Note that the patients included in the study of Dubois and colleagues (2000) did not have the pathological confirmation of corticobasal degeneration. Thus, it cannot be assumed that they all presented the pathology described above and their condition may be best referred to as the corticobasal

syndrome, which may present other pathological substrates, such as Alzheimer's disease, progressive supranuclear palsy and frontotemporal lobar degeneration (Ling et al., 2010; Lee et al., 2011). In progressive supranuclear palsy, there are pathological changes in brainstem nuclei, the basal ganglia, the cerebellum and the precentral gyrus (Dickson et al., 2010). Even an atypical variant of the disease associated with frontal lobe dementia shows cortical loss in the temporal, parietal and motor cortex, in addition to the prefrontal cortex (Bigio et al., 2001). Finally, frontotemporal dementia encompasses the large spectrum of non-Alzheimer dementias characterized by frontotemporal lobar degeneration (Pan et al., 2012), with atrophy often observed in the insular cortex and subcortical areas (Chow et al., 2008), as well as the parietal lobe (Whitwell et al., 2009).

In conclusion, the Frontal Assessment Battery has been validated on a sample of patients with various neurodegenerative syndromes that affect several cortical and subcortical brain structures and white matter tracts. Although there was probably degeneration of frontal cortex in many of these cases, the pathology was clearly not restricted to the frontal cortex, raising the question whether the cognitive impairments observed could be ascribed solely or even primarily to the frontal cortex damage. The difficulties in performance on the different FAB subtests might have been due to lesions in parts of the brain other than the frontal cortex and, most likely, the result of widespread cognitive dysfunction due to extensive brain damage.

Although one cannot question the usefulness of the Frontal Assessment Battery in assessing certain aspects of executive function on various populations of patients presenting with neurodegenerative diseases, it cannot be claimed that

the battery assesses "frontal" cortical dysfunctions until individuals with lesions restricted to the frontal cortex have been examined and shown to be impaired. Surprisingly, despite its publication more than 12 years ago, its wide clinical use, and its name implying assessment of frontal cortical function, the Frontal Assessment Battery has never been tested on a population of patients with lesions restricted to the frontal cortex. It has been mostly used to examine patients with Parkinson's disease (Cohen et al., 2012), various types of dementia (Lipton et al., 2005), neurological conditions such as stroke (Mok et al., 2004), or alcohol dependence (Zago-Gomes & Nakamura-Palacios, 2009). Among 148 recently reviewed studies that used the FAB, none of them examined its power in measuring deficits in patients with only frontal cortical damage. Until such a study is conducted, the widespread assumption that impairments observed on this battery are due to "frontal" cortical abnormality is not warranted.

The purpose of the present research was to examine performance on the FAB of patients who had sustained damage limited to the frontal cortex and no more than the immediately subjacent white matter. Only in this manner can one examine whether frontal cortical damage can yield impairments on the tasks that comprise the Frontal Assessment Battery.

Materials and methods

Participants

The participants were 45 patients from the Montreal Neurological Hospital who had unilateral brain surgery for the removal of a low-grade cerebral tumour or cortical excision for the relief of focal epileptic seizures, except for one patient

with a small excision involving the supplementary motor area bilaterally. A few patients had damage following a cerebrovascular accident. Twenty-five patients had excisions restricted to the frontal cortex: these excisions included frontal cortical removal and no more than the immediately subjacent white matter. In other words, these were patients in whom any observed functional impairment could be ascribed to frontal cortical damage. Fourteen patients had lesions in the left frontal cortex, ten had lesions in the right frontal cortex and one patient had bilateral frontal cortical damage in the supplementary motor area. All removals spared the primary motor cortical region on the precentral gyrus, except for two patients (Patients F005 and F017). Excisions in the left hemisphere always spared Broca's region on the inferior frontal gyrus. There were, however, two patients (Patients F017 and F024) who suffered a cerebrovascular accident involving this region. Nineteen of the patients had undergone neurosurgery for a tumour resection, three for the relief of idiopathic epilepsy, and three patients had suffered a cerebrovascular accident. On average, the frontal patients were tested 5.94 years (SD: 10.07) after their surgery or cerebrovascular accident, ranging from five months to 50 years.

The temporal group included 12 patients with left and eight patients with right) temporal lobe excisions. Eight of these patients had undergone neurosurgery for the removal of epileptogenic tissue (three left- and five right-sided excisions), 11 for a tumour removal (eight left- and three right-sided lesions) and one LT patient had suffered a cerebrovascular accident. The eight surgical removals of epileptogenic tissue involved either a selective amygdalo-hippocampectomy (n=6) in which these two medial temporal structures are

resected with relative sparing of the surrounding cortex, or an anterior temporal lobectomy (n=2) including the amygdala and the anterior part of the hippocampal formation. Of the eleven tumour resections, three were standard anterior temporal lobectomies, with the excision of the middle temporal gyrus in one case. Two patients underwent selective amygdalo-hippocampectomy. One tumour resection involved the posterior third of the inferior temporal gyrus, with slight extension on the middle temporal gyrus and into the white matter underlying the cortical excision. The anatomical data for the remaining five temporal tumour excisions and for the only patient with the cerebrovascular accident were not available, but there was confirmation from the neurosurgeon or neurologist that the lesion did not extend outside the temporal lobe. The time elapsed since the surgery or cerebrovascular accident for the temporal patients ranged from four months to 26 years and two months, with an average of 6.89 years (SD: 7.85). None of the patients had co-morbid neurological or psychiatric disorders. Only patients with a full-scale Wechsler IQ score above 80 were included in the study.

In addition, 25 healthy control participants were examined as a normal comparison group. These neurologically intact participants had no history of traumatic brain injury or psychiatric disorder and were recruited from relatives of the patients or the McGill University community.

Each temporal patient and healthy control participant was matched as closely as possible with one frontal patient for age and educational level. There was thus no significant difference between the three groups in age [$F(2, 67) = 1.335$, $P = 0.270$] and years of education [$F(2, 67) = 0.228$, $P = 0.797$]. In addition, there was no significant difference between the three groups in full-scale

IQ [F (2, 65) = 1.482 *P* = 0.235] and there was also no significant difference between the frontal and temporal patients for time since surgery [t (43) = 0.344, *P* = 0.733]. The characteristics of each group are presented in Table 1.

Table 1. Characteristics of participant groups

Group	Gender		Age	Education	Time since surgery (years)	Wechsler IQ
	M	F	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
F	8	17	51.4 (10.8)	15.4 (3.14)	5.94 (10.07)	110.38 (12.79)
LF	6	8	48.5 (11.24)	15.43 (3.25)	3.55 (3.43)	109.36 (12.91)
RF	2	8	55.2 (9.93)	15 (3.06)	8.70 (15.23)	110.78 (13.54)
BF	0	1	54 -	19 -	11.92 -	121 -
T	13	7	46.75 (11.34)	14.85 (2.37)	6.89 (7.85)	107 (11.55)
LT	8	4	44.42 (11.7)	15.5 (2.24)	5.69 (6.36)	107.73 (13.52)
RT	5	3	50.25 (10.5)	13.88 (2.36)	8.68 (9.88)	106 (8.93)
HC	9	16	51.84 (11.77)	15 (2.94)	- -	113.32 (11.75)

F = Frontal, LF = Left Frontal, RF = Right Frontal, BF = Bilateral Frontal, T = Temporal, LT = Left Temporal, RT = Right Temporal, HC = Healthy Control.

The study was approved by the Montreal Neurological Institute's Research Ethics Board and all participants gave informed consent.

Materials and procedure

The FAB was administered to the participants together with some other research tests. The FAB is divided into six subtests, each one intended to assess a 'function' thought to depend on the frontal cortex. The first subtest, 'conceptualization', examines verbal abstraction ability with three items of

similarities. For instance, participants are asked to tell in what way a banana and an orange are alike. In the second subtest, 'mental flexibility' is investigated by a one-minute trial of the phonological version of verbal fluency: participants have to tell as many words as they can, starting with a given letter of the alphabet (letter 's'). The third subtest examines the repetition of motor sequence, Luria's "fist-palm-edge" sequence, in order to assess 'action programming'. 'Sensitivity to interference' is measured in the fourth subtest of conflicting instructions in which subjects have to provide the opposite response to the examiner's signal: When the examiner claps once the subject must clap twice, and vice versa. 'Inhibitory control' of impulsiveness, the fifth subtest, is investigated by the go-no go paradigm, in which participants must inhibit a predominant response: The participants must clap once when the examiner claps once, but must not clap if the experimenter claps twice. Failures in this subtest occur when subjects clap in response to the examiner clapping twice, or when they continue to respond as in subtest 4. Finally, 'environmental autonomy' is examined by the capacity to inhibit a grasping response to stimulation of the palms by the examiner's hand.

Each subtest is scored from 0 to 3 based on the number of items completed correctly or the number of errors made, for a total score of 18 for the whole battery. A score of 3 indicates that there were no errors on that subtest. Scores of 1 or 2 are obtained when participants make errors, or fail to achieve the criteria for a full mark, such as generating less than 9 words, but more than 2 words, on the second subtest. Finally, a score of 0 is given when subjects cannot perform the task in a particular subtest or make more than a specified number of errors. The administration of the battery took approximately 10 minutes.

Results

Participants from all groups performed well on this battery. In all groups, most scores were 17 or 18 out of a possible total score of 18. In Figure 1, one can observe the substantial overlap in scores between the five participant groups.

Figure 1.

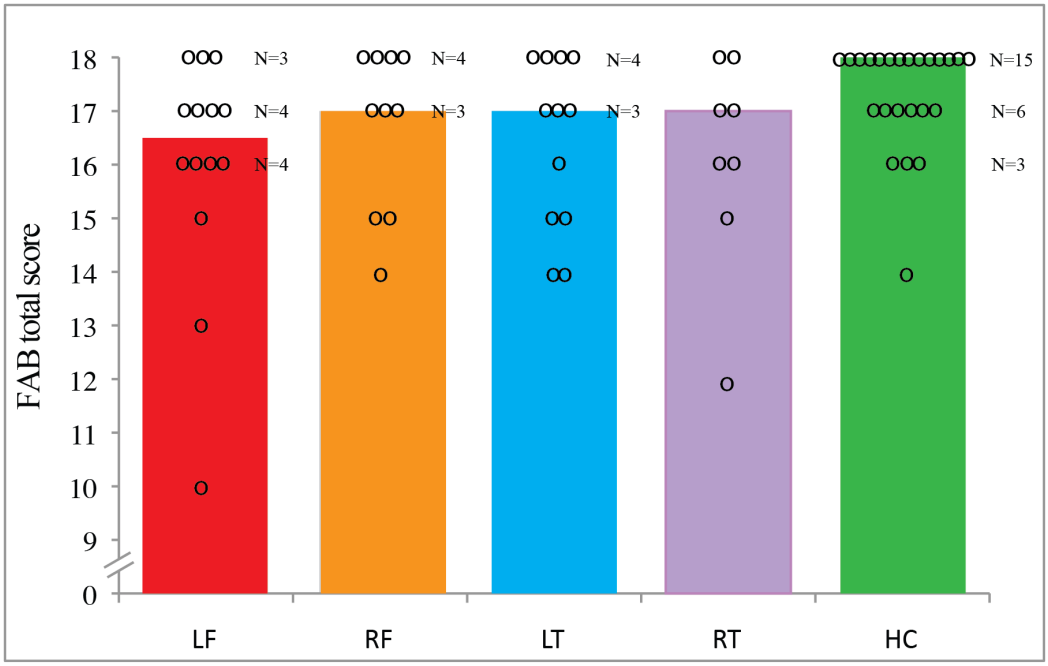


Figure 1. Median and individual Frontal Assessment Battery total score for each participant group. Circles represent individual participant scores. LF = Left Frontal; RF = Right Frontal; LT = Left Temporal; RT = Right Temporal; HC = Healthy Control

A chi-square test of independence breaking down the FAB scores into 8 categories, each representing an obtained FAB total score (‘18’, ‘17’, ‘16’, ‘15’, ‘14’, ‘13’, ‘12’ and ‘10’), indicated that there were no significant differences in

the FAB total score distribution between the five groups [χ^2 (28, n = 69) = 33.094, not significant (n.s.)]. A level of $P < 0.05$ was accepted as statistically significant. Because few participants obtained a total score of 14 or lower (see Figure 1), a second chi-square test was performed with the '14', '13', '12' and '10' categories collapsed into one '14 or lower' category, and again revealed the absence of significant differences in the FAB total score distribution between the five participant groups [χ^2 (16, n = 69) = 15.169, n.s.].

In addition to the chi-square test of independence, we also carried out a one-way analysis of variance (ANOVA) comparing the total FAB score between the five groups. This analysis yielded a marginally significant effect [F (4, 64) = 2.138, P = 0.086]. The left frontal group was significantly different from the control group according to the Dunnett test ($P = 0.042$). None of the other group differences were significant.

We also examined performance on each FAB subtest according to the four categories of score (3, 2, 1 and 0) using the chi-square test of independence. There were no significant differences between the five participant groups (left frontal, right frontal, left temporal, right temporal and healthy control groups), except for subtest 2 [mental flexibility; χ^2 (4, n=69) = 14.963, $P < 0.01$]. Patients with left frontal lesions performed significantly worse on this subtest than patients with right frontal lesions [χ^2 (1, n=24) = 8.571, $P < 0.01$], patients with right temporal lesions [χ^2 (1, n=22) = 4.197, $P < 0.05$] and healthy controls [χ^2 (1, n=39) = 9.032, $P < 0.01$]. Figure 2 shows the median and the distribution of scores for each participant group on subtest 2. Comparisons of the five groups on the other

FAB subtests did not yield any significant difference [χ^2 (4) = 2.863, n.s. for subtest 1; χ^2 (4) = 7.20, n.s. for subtest 3; χ^2 (4) = 3.985, n.s. for subtest 4; χ^2 (4) = 5.873, n.s. for subtest 5; χ^2 (4) = 4.919, n.s for subtest 6]. Note that the only patient with bilateral frontal lesion was excluded from these analyses. Table 2 shows the distribution of scores for the five groups on the six FAB subtests.

Figure 2.

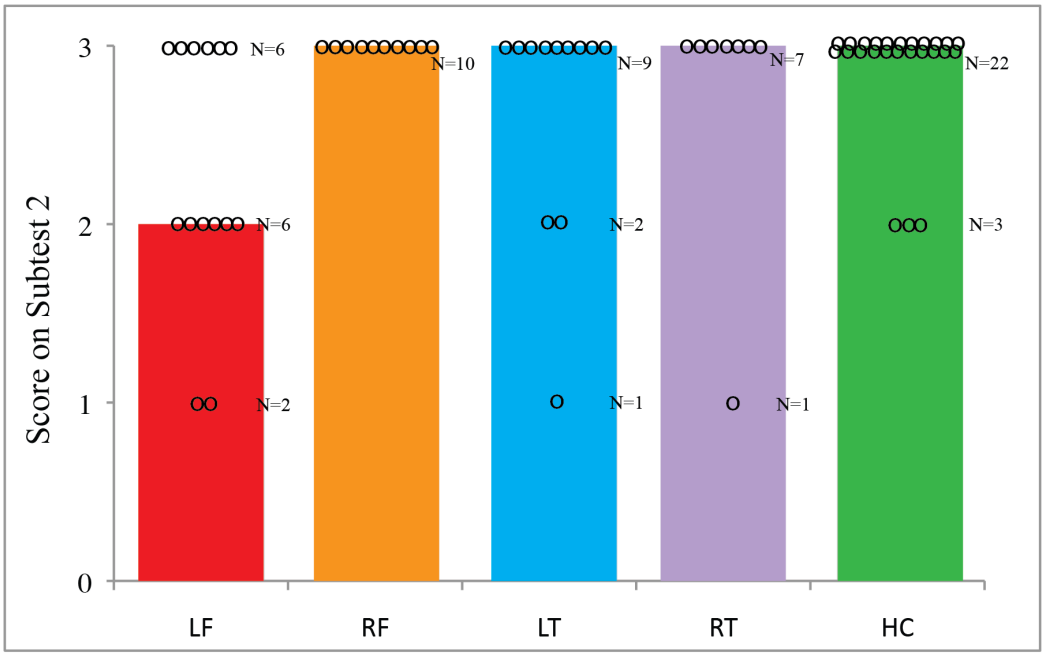


Figure 2. Median and distribution of scores for each participant group on the verbal fluency (mental flexibility) subtest of the FAB. Circles represent individual participant scores. LF = Left Frontal; RF = Right Frontal; LT = Left Temporal; RT = Right Temporal; HC = Healthy Control

Table 2. Number (and percent) of participants from each group obtaining scores of 3, 2, 1 or 0 on each subtest

Subtest 1. Conceptualization

Score	LF	RF	LT	RT	HC
3	12 (85.7%)	7 (70%)	10 (83.3%)	7 (87.5%)	23 (92%)
2	2 (14.3%)	2 (20%)	2 (16.7%)	0	2 (8%)
1	0	1 (10%)	0	1 (12.5%)	0
0	0	0	0	0	0

Subtest 2. Mental Flexibility

Score	LF	RF	LT	RT	HC
3	6 (42.9%)	10 (100%)	9 (75%)	7 (87.5%)	22 (88%)
2	6 (42.9%)	0	2 (16.7%)	0	3 (12%)
1	2 (14.3%)	0	1 (8.3%)	1 (12.5%)	0
0	0	0	0	0	0

Subtest 3. Action Programming

Score	LF	RF	LT	RT	HC
3	5 (35.7%)	5 (50%)	4 (33.3%)	4 (50%)	18 (72%)
2	7 (50%)	4 (40%)	5 (41.7%)	3 (37.5 %)	6 (24%)
1	1 (7.1%)	1(10%)	2 (16.7%)	1 (12.5%)	0
0	1 (7.1%)	0	1 (8.3%)	0	1 (4%)

Subtest 4. Sensitivity to Interference

Score	LF	RF	LT	RT	HC
3	13 (92.9%)	10 (100%)	12 (100%)	8 (100%)	25 (100%)
2	1 (7.1%)	0	0	0	0
1	0	0	0	0	0
0	0	0	0	0	0

Subtest 5. Inhibitory Control

Score	LF	RF	LT	RT	HC
3	13 (92.9%)	8 (80%)	11 (91.7%)	5 (62.5%)	23 (92%)
2	0	1 (10%)	1 (8.3%)	2 (25%)	2 (8%)
1	1 (7.1%)	1 (10%)	0	1 (12.5%)	0
0	0	0	0	0	0

Subtest 6. Environmental autonomy

Score	LF	RF	LT	RT	HC
3	13 (92.9%)	10 (100%)	12 (100%)	7 (87.5%)	25 (100%)
2	1 (7.1%)	0	0	0	0
1	0	0	0	1 (12.5%)	0
0	0	0	0	0	0

In additional analyses, the total number of words generated on subtest 2 was calculated for each participant. On average, patients in the left frontal group produced 10.14 words (SD: 4.57), patients in the right frontal group 14.4 words (SD: 1.78), patients in the left temporal group 11.58 words (SD: 3.82), patients in the right temporal group 13.88 words (SD: 4.36) and healthy control participants 16.8 words (SD: 5.17). Performance is shown in Figure 3. A one-way ANOVA showed a significant group difference in the mean number of words produced [$F(4,64) = 6.145$, $P < 0.001$]. Post-hoc Scheffe analyses revealed that both left frontal and left temporal groups generated significantly fewer words than the healthy control group ($P < 0.002$ and $P < 0.01$, respectively).

Figure 3.

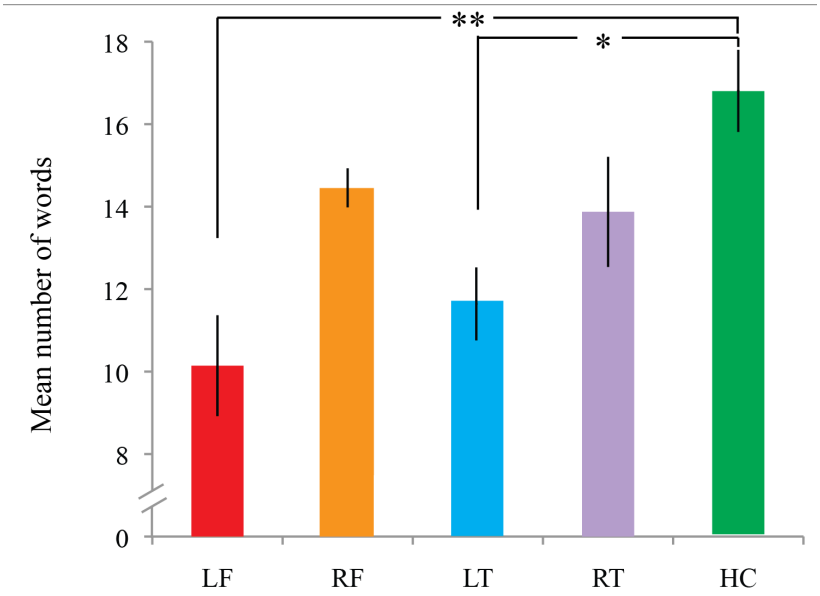


Figure 3. Mean number of words generated on the verbal fluency (mental flexibility) subtest of the FAB for each participant group. Error bars represent the standard error. ** $p < 0.001$, * $p < 0.05$ LF = Left Frontal; RF = Right Frontal; LT = Left Temporal; RT = Right Temporal; HC = Healthy Control

A Spearman correlation test examining the relationship between the FAB total score and time since surgery did not indicate a significant correlation (r_s = -0.220, P = 0.145).

Among the 14 patients with left frontal cortex lesions, eight of them (57.1%) were impaired on the verbal fluency subtest, that is, they had a score of 2 or lower, or generated 9 or fewer words (1.5 SD below the healthy control mean). Patient F026 produced only 10 words on the verbal fluency subtest and showed verbal fluency impairment on formal neuropsychological testing (score of 17 on the Chicago Word Fluency Test): she was therefore included in the impaired group, raising the proportion of impaired left frontal patients to 64.3%. A careful examination of the lesion location in the impaired versus unimpaired patients with left frontal lesions was carried out and is described below. Figure 4 shows the lesions of impaired left frontal patients and Fig. 7 shows the overlap of the lesions. Figures 5 and 7 show the lesions of the unimpaired patients with left frontal cortex lesions.

All patients with left frontal excisions that involved extensively the dorsal part of the medial frontal lobe above the anterior cingulate gyrus were impaired on the fluency subtest (Figs 4 and 7). We consider these cases individually below. Patient F018 had a resection that involved most of the supplementary motor area (SMA) and extended anteriorly to include the pre-SMA and nearby dorsomedial frontal cortex as far as the level of the genu of the corpus callosum. Ventrally, the excision involved the cortex in the adjacent cingulate sulcus, probably affecting the two posterior cingulate motor areas, and the paracingulate gyrus, but it did not involve the cortex on the cingulate gyrus per se (Fig. 4). In Patient F007, there

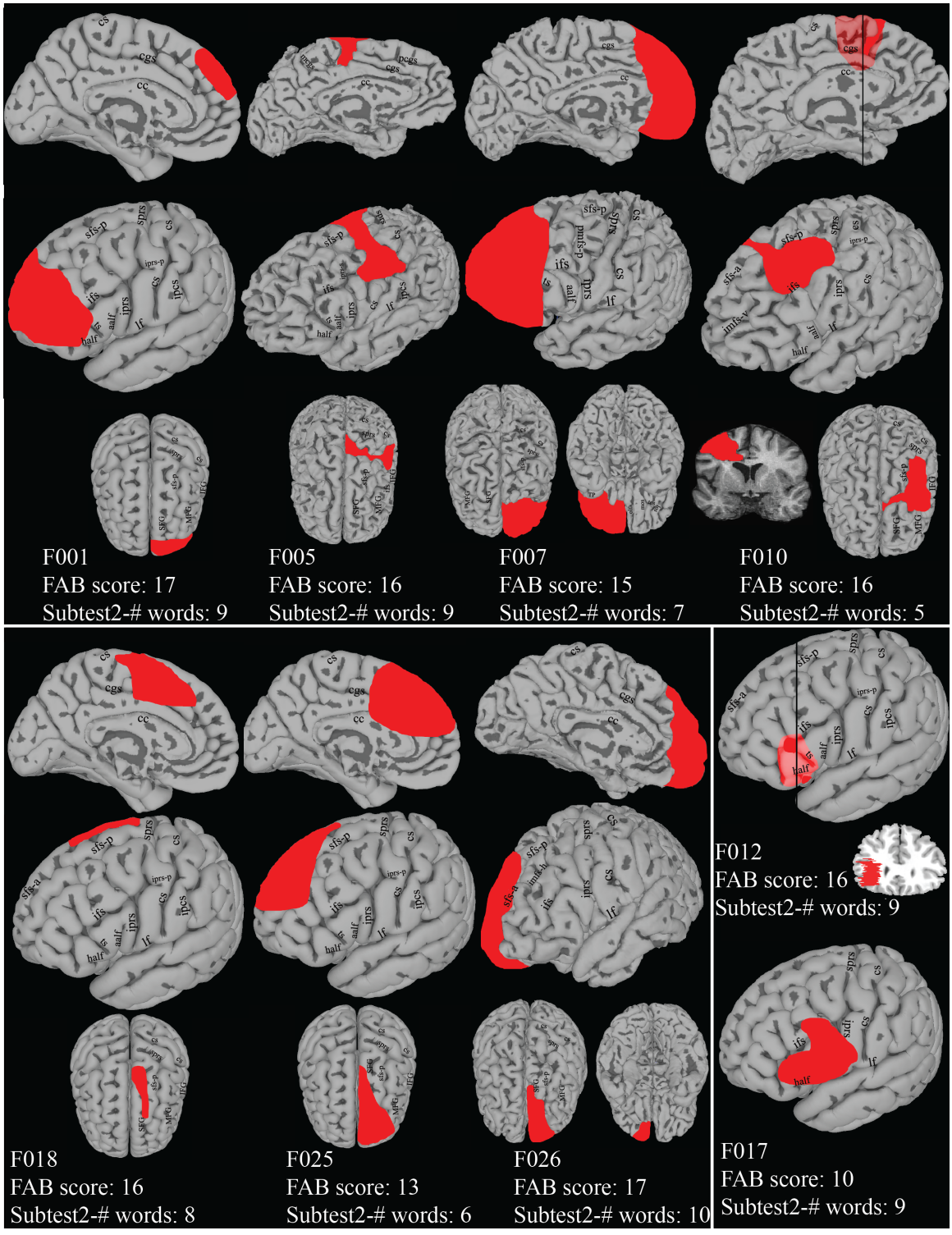

F001
FAB score: 17
Subtest2-# words: 9
F005
FAB score: 16
Subtest2-# words: 9
F007
FAB score: 15
Subtest2-# words: 7
F010
FAB score: 16
Subtest2-# words: 5
F012
FAB score: 16
Subtest2-# words: 9
F018
FAB score: 16
Subtest2-# words: 8
F025
FAB score: 13
Subtest2-# words: 6
F026
FAB score: 17
Subtest2-# words: 10
F017
FAB score: 10
Subtest2-# words: 9

Figure 4. The cortical lesions (in red) of the left frontal patients with impairment on the verbal fluency (mental flexibility) subtest of the FAB. The medial and lateral extents of the lesions are shown, as well as the ventral and dorsal views when relevant. The lesions are displayed on the 3D-reconstructions of the post-operative magnetic resonance images for Patients F005, F007, F010 and F026; and on the standard Montreal Neurological Institute (MNI) brain for Patients F001, F012, F017, F018 and F025. In the latter cases, tracings of the lesions were used with MRIcro software (Rorden & Brett, 2000) to display them on the MNI brain. Abbreviations: aalf = ascending anterior ramus of the lateral fissure; cc = corpus callosum; cgs = cingulate sulcus; cs = central sulcus; half = horizontal anterior ramus of the lateral fissure; IFG = inferior frontal gyrus; ifs = inferior frontal sulcus; imfs-v = intermediate middle frontal sulcus – vertical; ipcs = inferior post-central sulcus; iprs = inferior precentral sulcus; iprs-p = inferior precentral sulcus – posterior; iprs-s = inferior precentral sulcus – superior; lf = lateral fissure; los = lateral orbital sulcus; mcgs = marginal branch of the cingulate sulcus; MFG = middle frontal gyrus; mos = medial orbital sulcus; olfs = olfactory sulcus; pmfs = posterior middle frontal sulcus – posterior; SFG = superior frontal gyrus; sfs-a = superior frontal sulcus – anterior; sfs-p = superior frontal sulcus – posterior; sprs = superior precentral sulcus; tos = transverse orbital sulcus; TP = temporal pole; ts = triangular sulcus.

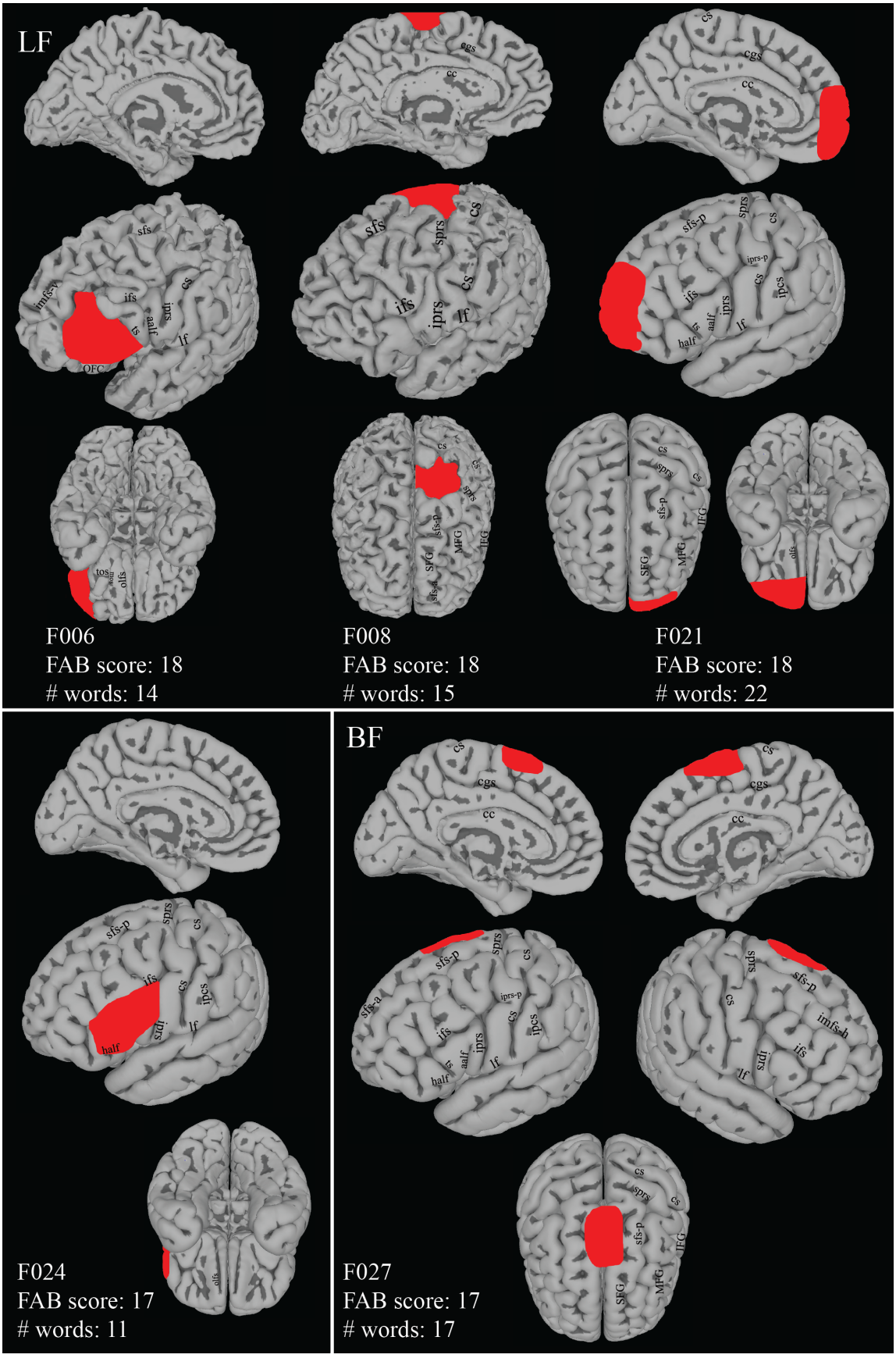

LF
F006
FAB score: 18
words: 14
F008
FAB score: 18
words: 15
F021
FAB score: 18
words: 22
F024
FAB score: 17
words: 11
BF
F027
FAB score: 17
words: 17

Figure 5. The cortical lesions (in red) of left frontal patients, including the bilateral frontal patient, who were not impaired on the verbal fluency (mental flexibility) subtest of the FAB. The medial and lateral extents of the lesions are shown, as well as the ventral and dorsal views when relevant. The lesions are displayed on the 3D-reconstructions of the post-operative MRI for Patients F006 and F008; and on the standard MNI brain for Patients F021, F024 and F027. In the latter cases, tracings of the lesions were used with MRIcro software (Rorden & Brett, 2000) to display them on the MNI brain. Note that the anatomical data for Patient F023 were not available. See Fig. 4 for label abbreviations. BF = bilateral frontal; imfs-h = intermediate middle frontal sulcus – horizontal; LF = left frontal; OFC, orbitofrontal cortex; sfs, superior frontal sulcus.

was extensive damage to the anterior part of medial frontal cortex as well as the genu of the corpus callosum. The excision continued posteriorly to include area 8 and the posterior extent of this lesion overlapped with the anterior extent of Patient F018, but spared the SMA. Thus, impairment on the verbal fluency task does not necessitate a lesion of SMA. Patient F025 is another example of impairment associated with removal of the whole anterior portion of the left medial frontal cortex, including the anterior part of the supplementary motor area (SMA), the pre-SMA, the anterior part of cingulate and paracingulate cortex, the anterior part of the body of the corpus callosum, but sparing the posterior part of SMA. In Patient F001, an anterior dorsomedial lesion caused impairment on the verbal fluency task. This patient had a complete removal of the lateral frontopolar region (area 10) as well as the medial extent of area 9. Similarly, Patient F026 had a resection in the dorsomedial frontal region involving the anterior part of the superior frontal and paracingulate cortex and she was impaired. More specifically, the medial extent of cortical areas 8, 9 and 10 anterior to the SMA, but not the SMA per se, were damaged. Patient F005 is a case of resection of the dorsolateral prefrontal cortex (posterior part of the superior and middle frontal gyri) with extension on the dorsomedial surface. The lesion invaded the supplementary motor area as well as part of the cingulate sulcus that would include at least one of the posterior cingulate motor areas. In Patient F010, the resection involved the posterior dorsolateral prefrontal cortex but invaded the subjacent white matter to include the portion of the corpus callosum just behind the genu. The white matter removal has disconnected the cingulate region and the adjacent dorsomedial area 8 from its inputs (see the coronal section and the shaded region on the medial

view in Fig. 4). This patient was impaired on the verbal fluency subtest. By contrast, a patient with a lesion (Patient F027; Fig. 5) that involved the most dorsal part of the SMA bilaterally but did not extend more ventrally or anteriorly in the dorsomedial frontal region was not impaired. Similarly, another lesion (Patient F008), which involved the SMA in the left hemisphere, but did not extend anteriorly to include the cingulate sulcus and area 8 medially, did not cause impairment on the verbal fluency subtest. In Patient F021, the excision involved the whole frontopolar region (lateral, medial and orbital surfaces) but did not extend posteriorly in medial areas 9 and 8 or the SMA. This patient performed well on verbal fluency. In conclusion, it is clear that the critical region for the verbal fluency impairment is the dorsomedial frontal region above the anterior part of the cingulate region. Lesions restricted to SMA are not sufficient to cause the impairment.

Only two patients (Patients F012 and F017) had impairment on the verbal fluency subtest without damage to the left dorsomedial prefrontal cortex. Patient F012's lesion included the most rostral part of the insula, the entire pars orbitalis region (area 47/12) and, rostrally, the white mater of the anterior part of the pars triangularis, thus disconnecting the pars triangularis. Patient F017 suffered a cerebrovascular accident that involved the left pars opercularis and pars triangularis of the inferior frontal gyrus, thus Broca's area. It extended posteriorly on the anteriormost part of the precentral gyrus and dorsally on the adjacent middle frontal gyrus. Interestingly, this is the only frontal patient who performed poorly on the FAB. Neither Patient F012 nor F017 were aphasic at the time of testing. Note that two patients with lesions restricted to the inferior frontal gyrus

anterior to (Patient F006) or encompassing (Patient F024) Broca's areas 44 and 45, were not significantly impaired on the subtest. Patient F024 was a case of cerebrovascular accident, which after recovery from aphasia had no problem with verbal fluency. The medial frontal cortex of these two patients was well preserved. The anatomical data for the non-impaired Patient F023 were not available.

None of the ten cases with right frontal cortical excisions, even those that involved the entire prefrontal cortex (e.g., Patient F028; Fig. 6), was impaired on the verbal fluency task. Figure 7 shows the overlap of lesions for the RF patients. For two of the right frontal cases (Patients F015 and F022), we did not have access to the magnetic resonance images of the lesions; the operation report of Patient F015 specified a corticectomy of the mid-supplementary motor area of the superior frontal gyrus extending 4 cm in the rostral-caudal axis and 2.5 cm in the dorsal-ventral axis.

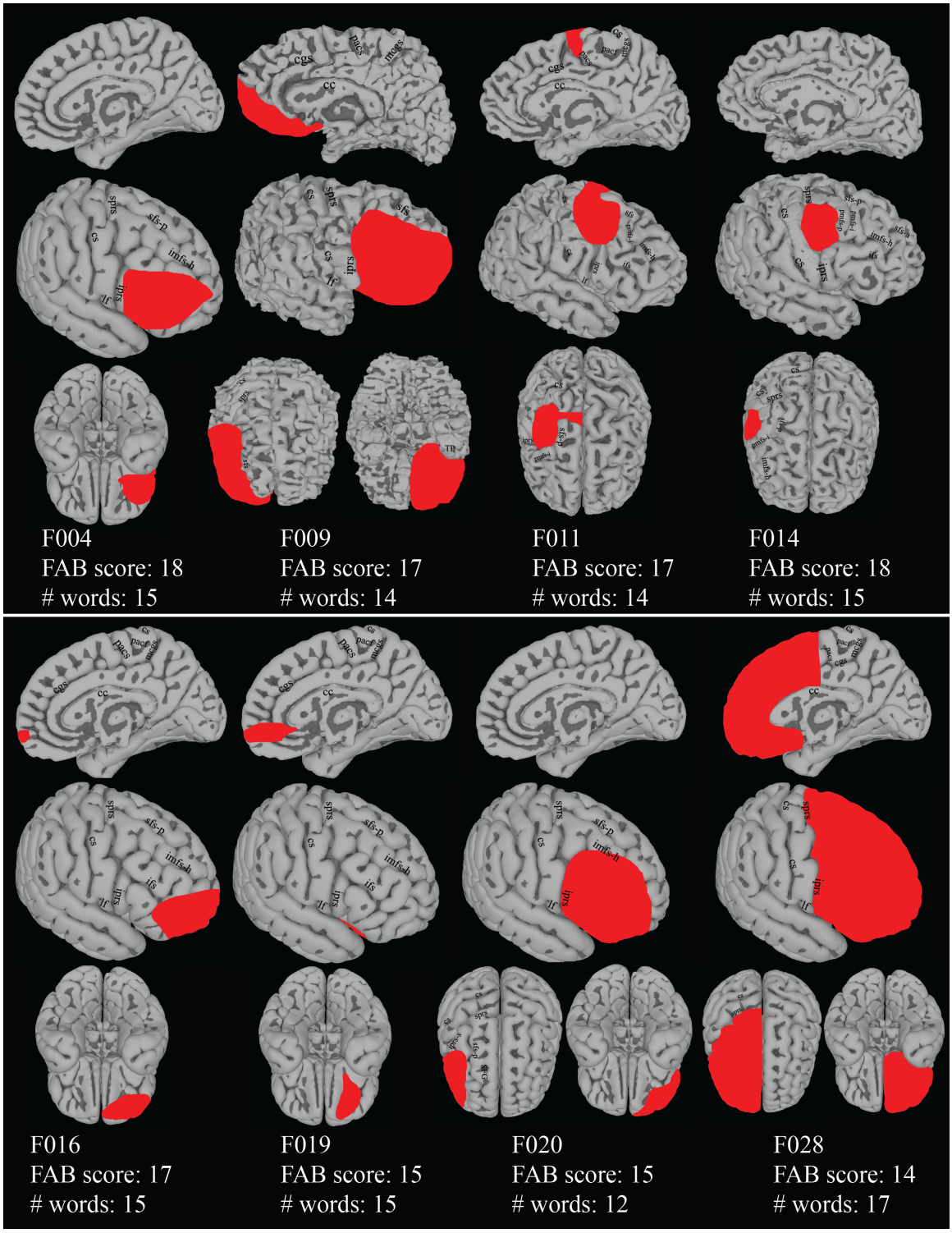

F004
FAB score: 18
words: 15
F009
FAB score: 17
words: 14
F011
FAB score: 17
words: 14
F014
FAB score: 18
words: 15
F016
FAB score: 17
words: 15
F019
FAB score: 15
words: 15
F020
FAB score: 15
words: 12
F028
FAB score: 14
words: 17

Figure 6. The cortical lesions (in red) of the right frontal patients who were not impaired on the verbal fluency (mental flexibility) subtest of the FAB. The medial and lateral extents of the lesions are shown, as well as the ventral and dorsal views when relevant. The lesions are displayed on the 3D-reconstructions of the post-operative MRI for cases F009, F011 and F014 and on the standard MNI brain for cases F004, F016, F019, F020 and F028. In the latter cases, tracings of the lesion were used with MRIcro software (Rorden & Brett, 2000) to display them on the MNI brain. The anatomical data for Patients F015 and F022 were not available. See Fig. 4 for label abbreviations. imfs-h = intermediate middle frontal sulcus – horizontal; pacf = paracentral fissure; pacs = paracentral sulcus; pmfs-i = posterior middle frontal sulcus – intermediate; pmfs-p = posterior middle frontal sulcus – posterior; sfs = superior frontal sulcus.

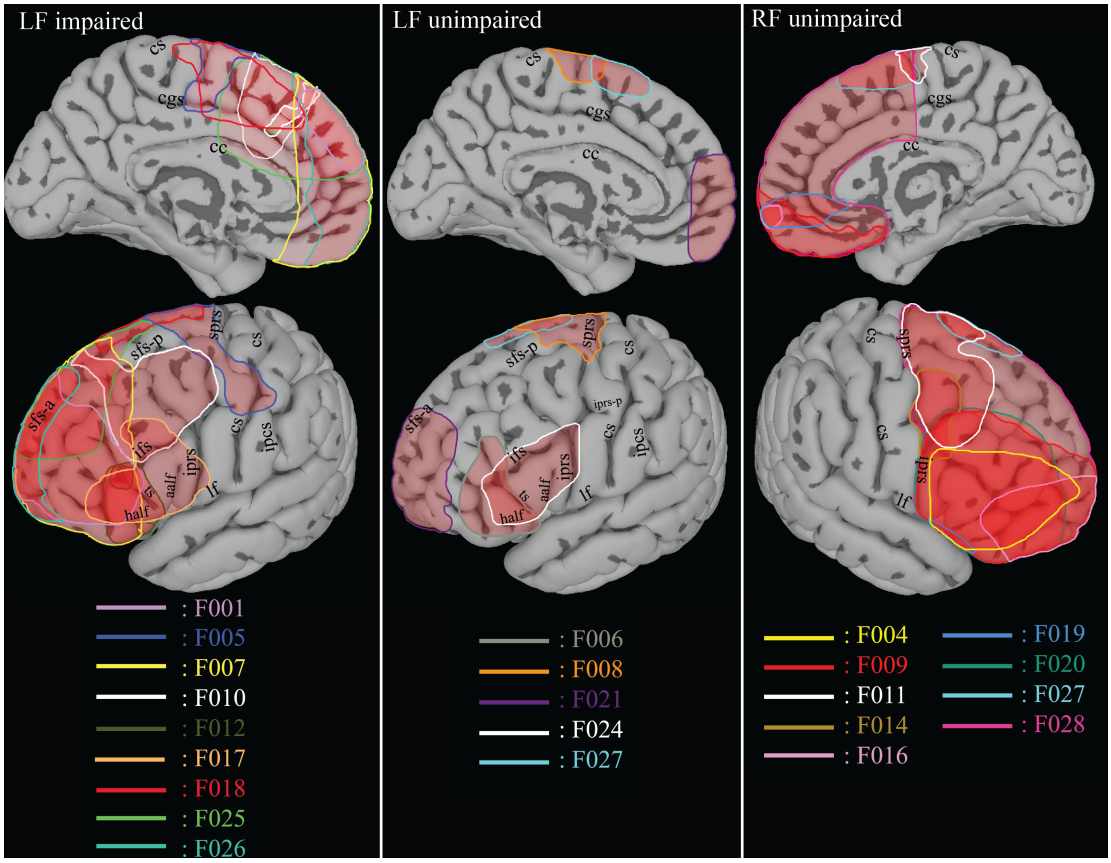


Figure 7. The overlap of the individual lesions displayed on the standard MNI brain for the left frontal patients impaired on the verbal fluency (mental flexibility) subtest of the FAB (*left*), for unimpaired left frontal patients (*middle*), and for unimpaired right frontal patients (*right*). See Fig. 4 for label abbreviations. LF = left frontal; RF = right frontal.

We also carried out a voxel-based lesion-symptom mapping analysis using MRIcron and NPM (www.mricro.com/mricron and www.mricro.com/npm, versions of 12/2012; Rorden, Karnath & Bonilha, 2007) in order to examine the relationship between lesion localization and impairment on the verbal fluency subtest in the left frontal patients. With this technique, the behavioural measure was entered as binomial data (i.e. impaired vs. non-impaired) for each participant. For each voxel, patients were divided into two groups according to whether or not there was a lesion in this voxel. Then, the binomial Liebermeister test (Rorden et al., 2007) was applied to compare performance for each affected voxel. Only voxels that were included in the lesions of at least three patients were included in the analysis. Although none of the voxels survived the strict corrections implemented in the software (permutation thresholding and false discovery rate thresholding), an uncorrected threshold with $L > 1.65$ and $P < 0.05$ indicated that voxels in the left anterior dorsomedial frontal region were significantly more affected in left frontal patients impaired on the verbal fluency subtest than in left frontal patients with normal performance. The map of significantly affected voxels when uncorrected thresholds are applied is shown in Fig. 8. These results corroborate the conclusion of our case-by-case analysis of the location of the lesions that are critical for an impairment on the verbal fluency subtest.

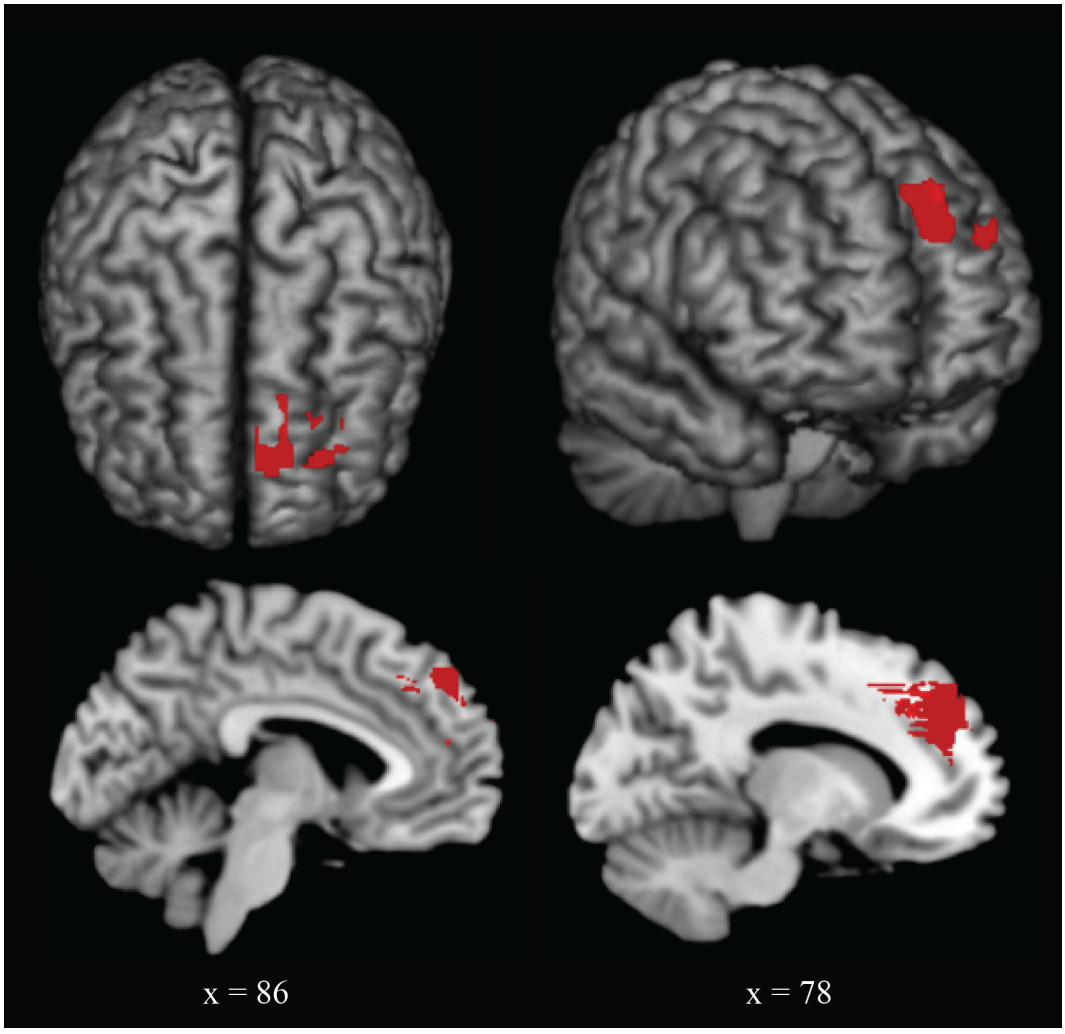


Figure 8. Statistical map of the voxel-based lesion-symptom mapping analysis, shown on the three-dimensional views (*top*) and two representative sagittal views of the MNI brain. The red areas represent voxels with significant L values at $P < 0.05$, using the uncorrected threshold.

Discussion

In order to conclude that a cognitive task measures aspects of the function subserved by a specific brain region, impairment on the task must be shown to be due to dysfunction restricted to this brain region and, ideally, dissociated from abnormalities occurring in another region of the brain (Teuber, 1955). The results of the present investigation demonstrate that performance on the FAB is not impaired by lesions restricted to the frontal cortex, except for performance on the verbal fluency (mental flexibility) subtest, which is impaired by left frontal lesions. Thus, the present data do not support the claim that the Frontal Assessment Battery is a sensitive test of frontal cortical dysfunction. It is interesting to note that the total FAB score (mean: 16.32, SD: 1.89) of the present patients with lesions restricted to the frontal cortex is clearly higher than that of the patients investigated in other studies, such as in the seminal study by Dubois and colleagues (2000), in which the average FAB total score across all neurological conditions was 10.3 (SD: 4.7). The lower score of these patients who presented with different neurological conditions affecting widespread regions of the brain suggests that the observed impairment was not due to the frontal cortex damage. The impairment on the FAB was more likely the result of a general cognitive dysfunction due to the extensive brain damage associated with their neurodegenerative conditions. In conclusion, while the 'Frontal' Assessment Battery might be a good screening tool to detect executive problems in neurodegenerative diseases, it cannot be said to be a measure that is sensitive to frontal cortex dysfunction. Consequently, deficits on the FAB found in some patient populations cannot be attributed exclusively to frontal cortex dysfunction.

It should be noted that the present group of frontal patients was typical of the frontal groups previously shown to be impaired on particular tasks at the Montreal Neurological Institute (e.g., Petrides & Milner, 1982; Thaiss & Petrides, 2008; Tsuchida, Doll & Fellows, 2010). Impaired performance on specific frontal tasks but normal performance on the FAB was also observed in several of the tested patients. For instance, on an active controlled memory retrieval test based on functional neuroimaging findings (Kostopoulos & Petrides, 2003), 11 of the 22 frontal patients who were not impaired on the FAB exhibited an impairment (Chapados & Petrides, unpublished results). Other interesting dissociations were observed: Two patients with good FAB scores (17/18 and 15/18) were impaired on the Wisconsin Card Sorting Test (only 3 categories completed and many perseverative errors). One patient with a perfect score on the FAB was able to complete 6 categories of the WCST, but required 127 cards and he committed 27 perseverative errors. Another patient performed well on the WCST (6 categories in 87 cards), but had a lower score on the FAB (14/18). Although WCST data were not available for all our patients, these results show that performance on the WCST and the FAB are not necessarily related.

One subtest of the Frontal Assessment Battery was found to be sensitive to dysfunction restricted to the left dorsomedial frontal cortex. This test referred to as the *mental flexibility* subtest examines verbal fluency, namely the generation of as many words as possible beginning with a particular letter of the alphabet (the letter 's') in 60 seconds. This subtest was the only one of the six FAB subtests to show both sensitivity and specificity to left dorsomedial frontal cortex dysfunction. These results are consistent with previous research that demonstrated

impairment on verbal fluency following left frontal lobe damage (Milner, 1964; Benton, 1968; Perret, 1974; Stuss et al., 1998; Baldo, Shimamura, Delis, Kramer, & Kaplan, 2001; Henry & Crawford, 2004; Robinson, Shallice, Bozzali & Cipolotti, 2012). In the present study, none of the excisions in the right prefrontal cortex, even those encompassing the entire right frontal cortex (see Patient F028, Fig. 6), resulted in impairment on this verbal fluency test. Thus, only certain parts of the frontal lobe in the language-dominant left hemisphere are necessary for word generation in a fluency task.

The present investigation has enabled us to provide a more precise localization of the source of the verbal fluency impairment within the left frontal lobe by examining the locus of the lesion and the score of the individual patients (see Fig. 4). This examination showed that lesions restricted to the anterior frontal region and the orbitofrontal region in the left hemisphere do not lead to impairment on verbal fluency. Dorsomedial lesions that included the cortex extending above the anterior cingulate region as far as the midline were the ones most likely to lead to impaired verbal fluency. However, damage restricted to the supplementary motor area (SMA) was not sufficient to cause impairment on the verbal fluency task. The lesion had to be larger than the SMA and to include the cortex anterior and ventral to it. It thus appears that the dorsomedial frontal cortex anterior to the SMA, including the pre-supplementary motor area (pre-SMA) and the adjacent ventrally located cingulate motor areas, was the focus of this verbal fluency impairment. In this respect, it is interesting to note that Stuss and colleagues (1998) reported a moderate impairment on a phonemic verbal fluency

task in patients with superior medial frontal damage, but failed to find such impairment in patients with bilateral orbital frontal lesions (Stuss et al., 1986).

The dorsomedial frontal cortex comprises the medial extension of the Brodmann cytoarchitectonic areas 6, 8, and 9 on the medial wall of the superior frontal gyrus, and more ventrally the paracingulate cortex (area 32) which constitutes a transitional zone just above the agranular anterior cingulate cortex (Petrides & Pandya, 1999). The posterior dorsomedial frontal cortex in front of the foot area of the primary motor cortex comprises the supplementary motor complex (Nachev et al., 2008). Ventrally and anteriorly, towards the cingulate sulcus, it is replaced by the cingulate motor areas (Amiez & Petrides, 2012). The supplementary motor complex and cingulate motor areas are strongly interconnected with components of the motor system, including the primary motor cortex, the basal ganglia, the cerebellum and the spinal cord (Jürgens, 1984). It has been argued that the SMA complex may play a role in the initiation, elaboration and control of intentional actions, including speech (see reviews by Goldberg, 1985 and Nachev et al., 2008). Penfield and Welch (1951) were the first to suggest the existence of a speech representation area in this region based on the observation of vocalization and inhibition of voluntary speech ('speech arrest') upon stimulation of the SMA of the dominant hemisphere.

Several of the left frontal patients showing impairment on the verbal fluency task had damage in cortex located ventral to the SMA and extending anteriorly. This corresponds to cortex in the cingulate sulcus and the paracingulate cortex where a recent anatomo-functional study (Amiez & Petrides, 2012) showed the existence of three distinct motor areas. All three areas appeared to be

somatotopically-organized and to include a region activated by tongue movements, thus suggesting the existence of a face/mouth representation, potentially involved in some aspects of language production. This is further corroborated by a positron emission tomography study showing speech activation foci in the middle portion of the anterior cingulate region (Paus, Petrides, Evans & Meyer, 1993).

Clinical reports of patients who had undergone medial frontal surgery encompassing the SMA proper, and often extending beyond its limits anteriorly and ventrally, refer to transient reduction of spontaneous movements (Bannur & Rajshekhar, 2000) and expressive speech (Rostomily, Berger, Ojemann & Lettich, 1991; Ackermann, Daum, Schugens & Grodd, 1996; Zentner, Hufnagel, Pechstein, Wolf & Schramm, 1996; Krainik et al., 2001, 2003). There was often disruption in the initiation of spontaneous speech, ranging from mutism to word-finding difficulties and hesitancy, which usually resolved over several months (Krainik et al., 2001). Zentner and colleagues (1996) reported long-lasting impairment in complex or high-speed speech tasks, such as verbal fluency. Speech reduction occurred in patients whose superior medial resection included at least 16% of the area activated during a pre-operative functional magnetic resonance imaging semantic fluency task (Krainik et al., 2003).

The literature on the syndrome following infarction in the territory of the left anterior cerebral artery also provides relevant information on the role of the superior medial frontal cortex in speech. Transcortical motor aphasia, characterized by limited spontaneous speech but intact repetition, articulation, comprehension and object naming (Freedman, Alexander & Naeser, 1984), has

been linked to damage of the left medial frontal cortex including, but extending beyond, the SMA (Rubens, 1975; Madseu, Schoene & Funkenstein, 1978; Racy, Jannotta & Lehner, 1979; Alexander & Schmitt, 1980; Ross, 1980; Goldberg, Mayer & Toglia, 1981; Freedman et al., 1984; Ziegler, Kilian & Deger, 1997; Pai, 1999). When assessed, verbal fluency, especially in the phonological condition, was always low in these patients (Ziegler et al., 1997). Together, these findings suggest that the dorsomedial frontal region that includes the supplementary and cingulate motor regions play a role in the initiation and emission of intentional speech, which might be necessary to perform successfully a verbal fluency task.

In the past, the importance of negative results in neuropsychological testing, i.e. concluding that a given cognitive function is not dependent upon a specific brain region, has been highlighted by Hebb (1945) who refuted the then-common view that frontal lobe damage was associated with deterioration of intellectual function as measured by standard intelligence tests (Hebb, 1939, 1945). The relationship between 'frontal functions' and 'executive functions' requires some discussion. These terms, which are often used interchangeably should not be considered synonymous, as suggested by the results of this and other recent studies, which have shown widely used "executive function" tests not to be specific to the frontal cortex. For instance, the Category Test and Part B of the Trail Making Test (Reitan & Wolfson, 1995), the number of total correct designs on a design fluency task (Possin et al., 2009), the color-word interference condition of the Stroop Test (Heflin et al., 2011), or a scale composed of different executive function subtests (Carey et al., 2008), have been shown unable to differentiate frontal from nonfrontal patients, or shown to be related to

dysfunction in frontal subcortical structures and in posterior cortex in addition to frontal cortex. The present study adds to this growing body of literature indicating that frontal function and executive function are not synonymous.

In the present study, only phonological verbal fluency (mental flexibility) subtest was shown to be sensitive to injury of the frontal cortex, specifically the dorsomedial frontal cortical region in the left hemisphere. These findings underlie the importance of validating tests on patients with lesions restricted to the region of interest in order to make claims about the functions of a specific cortical region.

Connecting text – Study 1 to Study 2

The Frontal Assessment Battery was designed to assess so-called 'frontal' functions (Dubois et al., 2000), based on the assumption that the frontal lobe, and therefore the frontal cortex, generally support executive functions and that a dys-executive syndrome identified by this battery reflects frontal dysfunctions. In Study 1, we found that the FAB globally as well as five of its six subtests were not sensitive to damage restricted to the frontal cortex (Chapados & Petrides, 2013). Damage limited to the frontal cortex did not lead to generalized executive dysfunction as measured by this battery. The fact that this battery commonly associated with frontal functions is not impaired by frontal cortex damage suggests that other general measures of executive functions or behavioural markers commonly associated with the frontal cortex might also not be sensitive to such damage. In Study 2, we examined whether the patients with frontal cortex lesions studied in Study 1 demonstrated utilization behaviour, a type of dysfunctional behaviour that has been described as resulting from frontal lobe damage (Lhermitte, 1983).

Study 2

Utilization Behaviour after Lesions Restricted to the Frontal Cortex

Catherine Chapados and Michael Petrides

This work is in press at *Neuropsychologia*.

Abstract

Utilization behaviour, which refers to the tendency of patients to use objects presented to them out of context and in the absence of instructions to use them, has been ascribed to dysfunction of the frontal cortex. However, careful examination of the reports of patients presenting with utilization behaviour shows that these patients had sustained widespread cerebral lesions extending beyond the frontal cortex and often involving massive subcortical damage. The present study examined whether utilization behaviour can be observed in patients with lesions restricted to the prefrontal cortex and no more than the immediately subjacent white matter. All patients had surgical excisions, except for three patients in the frontal group who had sustained a cerebrovascular accident. A group of patients with excisions in the temporal lobe and a group of healthy participants were also studied for comparison. The investigation of utilization behaviour took place in the context of a broader neuropsychological examination. There was no difference in the presence of utilization behaviour in patients with lesions restricted to the prefrontal cortex in comparison with patients with temporal lobe lesions and carefully matched neurologically intact individuals. The results suggest that, in previous studies, the exhibition of utilization behaviour by patients with extensive damage to the anterior part of the brain may have been due to damage to subcortical structures or to the prefrontal cortex in conjunction with subcortical damage.

Introduction

In the search for markers of frontal cortical dysfunction, Lhermitte (1983) ascribed a particular problem that he named 'utilization behaviour' to damage of the frontal lobe. He defined utilization behaviour as the automatic instrumentally correct, but contextually inappropriate, motor response to environmental stimuli. It is elicited by presenting everyday objects in front and within the reach of patients or in the hands of patients without providing any instructions. For instance, when presented with a water carafe and a glass and given no instructions, the individual exhibiting utilization behaviour will pour water into the glass and drink.

In the first report by Lhermitte (1983), patients with various neurological conditions, including glioma, aneurysms and Alzheimer's disease, leading to damage assumed to affect the frontal lobes exhibited utilization behaviour. Anatomical information was provided for five cases of utilization behaviour, all of which presented massive damage to the anterior part of the brain extending well beyond the frontal cortex and involving the corpus callosum, the basal ganglia, projection fibers and parts of the parietal and temporal lobes. On the basis of these cases, Lhermitte attempted to ascribe utilization behaviour to specific parts of the frontal cortex, but admitted that it was impossible to define precisely the responsible frontal structures and raised the issue of the potential involvement of subcortical structures, especially the caudate nucleus.

Lhermitte and colleagues (1986) later observed utilization behaviour in patients with lesions overlapping in the inferior half and the mediobasal area of the frontal lobes, including subcortical structures. This behaviour was also

observed in two patients with deep structure damage, including the thalamus, the internal capsule and the caudate nucleus, in 10 patients with Alzheimer's disease, and in a few patients with other diffuse neurological conditions.

Two additional group studies on utilization behaviour were later published. In one study comparing patients with frontal damage with patients who had lesions outside the frontal lobe, utilization behaviour was observed in only two out of 52 frontal patients (De Renzi et al., 1996). One had suffered an infarct in the region of the cingulate gyrus and the other had a lesion on the medial and lateral aspects of the frontal lobes also affecting the subventricular zone. Clearly the two patients exhibiting utilization behaviour did not have lesions restricted to the frontal cortex. The other group study showed utilization behaviour in six patients assumed to have damage to the frontal lobe. However, the damage was the result of frontotemporal dementia in two cases, and extended outside the frontal lobe in the other four cases involving significantly subcortical structures or other cortical areas (Besnard et al., 2009). The investigators concluded that they could not ascribe utilization behaviour to the frontal cortex per se given the extensive and diffuse cortico-subcortical damage in the patients studied.

Since the original publications, several single case reports of utilization behaviour pointed to different parts of the frontal cortex in combination with disruptions of cortico-cortical and cortico-subcortical connections, cortical areas outside the frontal lobe, or combinations of these as being responsible for utilization behaviour. Shallice and colleagues (1989) observed utilization behaviour in a patient with bilateral inferior medial frontal lesion that extended posteriorly and subcortically to invade the rostrum of the corpus callosum, the

internal capsule bilaterally and the right head of the caudate nucleus and putamen. In other single case studies, the dorsomedial frontal cortex, including the supplementary motor area and the cingulate cortex, was often involved, unilaterally (Boccardi et al., 2002), bilaterally (Fukui et al., 1993; Brazzelli et al., 1994; Brazzelli & Spinnler, 1998), in combination with underlying white matter tracts (Laplane et al., 1981; Ishihara et al., 2002) and the head of the caudate nucleus (Degos et al., 1993), or in combination with the posterior part of the superior and middle temporal gyri (Assal, 1985). Utilization behaviour was also observed in cases of bilateral damage to the medial aspect of both the frontal and temporal lobes (Brazzelli et al., 1994; Brazzelli & Spinnler, 1998; Balani et al., 2009). Other single case studies reported utilization behaviour without frontal cortex damage, but following damage to subcortical structures interconnected with the frontal cortex, such as the bilateral paramedian thalamic region (Eslinger et al., 1995), the right ventroanterior and intralaminar nuclei of the thalamus (Hashimoto et al., 1995), and the right caudate nucleus (Rudd et al., 1998).

It is clear from close examination of the studies reported above that utilization behaviour after frontal damage was always accompanied by widespread subcortical damage. It is therefore not possible to link utilization behaviour to frontal cortical damage from these data. Can utilization behaviour result from lesions restricted to frontal cortical damage, without subcortical or extra-frontal damage? This study is the first attempt to examine this question by examining utilization behaviour in a large group of patients with well-documented lesions restricted to the frontal cortex and no more than the immediately subjacent white matter and by comparing the frequency of utilization behaviour between the

frontal and a control group of patients with damage in another part of the brain, namely the temporal lobe.

Materials and Methods

Participants

Thirty-six patients with brain lesions participated in this study. The frontal group included 20 patients (13 females) with lesions restricted to the frontal cortex and no more than the immediately subjacent white matter. Nine of these patients had left-sided lesions, 10 had right-sided lesions and one had a small bilateral excision of the dorsal part of supplementary motor area. In the frontal group, 13 patients had undergone a tumour excision, four had surgical excision for the relief of epilepsy, and three had suffered a cerebrovascular accident. All lesions spared the motor cortex of the precentral gyrus. The time elapsed since the surgery or cerebrovascular accident ranged from 11 months to 50 years with an average of 7.82 years (SD: 10.84). The temporal lobe group comprised 16 patients (six females) who had undergone surgery in the temporal lobe for the removal of a cerebral tumour (n = 9) or surgical excision for the relief of focal epileptic seizures (n = 7). Ten patients had left-sided and six had right-sided excisions. On average, the patients with temporal lesions were tested 6.93 years (SD: 7.00) after their surgery, ranging from four months to 17 years and six months. None of the patients in the frontal or temporal groups had a co-morbid neurological or psychiatric disorder.

In addition, 20 healthy control participants (14 females) were included in the study as a comparison group. They were relatives of the patients or members

of the McGill University community with no history of neurological disorder, or psychiatric disorder. Only participants with a full-scale Wechsler Abbreviated Scale of Intelligence (WASI) IQ score over 79 were included. All participants were right-handed, with the exception of one left-handed patient in the frontal group (F015), one ambidextrous patient in the temporal group (T003) and two left-handed control subjects (C013 and C038). Each participant in the temporal and healthy control groups was matched as closely as possible with one patient in the frontal group for age and education. The three groups did not significantly differ in terms of age [$F(2, 53) = 1.191$, $p = 0.312$], years of education [$F(2, 53) = 0.065$, $p = 0.937$], and IQ [$F(2, 52) = 0.885$, $P = 0.431$]. There was also no significant difference between the frontal and temporal patients for time elapsed since injury [$t(34) = 0.285$, $P = 0.778$]. Characteristics of the three groups are presented in Table 1.

Table 1. Characteristics of participant groups

Group	Gender		Age (years)	Education (years)	Time since surgery (years)	Wechsler IQ
	M	F	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Frontal	7	13	53.15 (9.92)	15.05 (3.44)	7.82 (10.84)	107.58 (15.19)
Left	4	5	52.22 (9.02)	15.11 (3.69)	5.01 (4.42)	106.56 (14.16)
Right	3	7	53.9 (11.57)	14.6 (3.31)	9.55 (14.89)	107.11 (17.16)
Bilateral	0	1	54 -	19 -	11.92 -	121 -
Temporal	10	6	48.56 (10.87)	14.88 (2.39)	6.93 (7.00)	107.44 (12.51)
Left	6	4	45.9 (12.66)	15.3 (2.41)	7.48 (6.82)	108.5 (13.99)
Right	4	2	53 (5.29)	14.17 (2.4)	6.74 (8.01)	105.67 (10.54)
Control	6	14	53.65 (11.15)	14.7 (3.16)	- -	112.45 (12.44)

The extent and precise location of the frontal lesions were assessed from magnetic resonance imaging (MRI) scans when available or from tracings of the lesions by an experienced neurologist based on the post-operative computed tomography scan or MRI. The lesions were manually drawn from the native space to the standard Montreal Neurological Institute (MNI) brain with MRIcro software (Rorden & Brett, 2000). Eight temporal patients underwent an excision of the anterior medial temporal lobe region: six of them had a selective amygdalo-hippocampectomy in which these medial temporal lobe structures were resected with the surrounding cortex, and two patients had a resection of the anterior medial temporal cortex including the amygdala and the anterior part of the hippocampal formation, with additional removal of the middle temporal gyrus in one case. One patient had a resection in the posterior third of the inferior temporal gyrus. The anatomical data for the remaining seven temporal patients were not available, but there was confirmation from the neurosurgeon that the excisions were confined to the temporal lobe.

The study was approved by the Montreal Neurological Institute's Research Ethics Board and all subjects gave informed consent.

Materials and procedures

There are two procedures proposed in the literature to elicit utilization behaviour (Lhermitte, 1983; Shallice et al., 1989). The method used by Lhermitte was, first, to provoke the grasp reflex by stimulating the participant's palm and fingers with the objects and, then, to continue the stimulation with various

utilitarian objects for approximately 30 sec. The examiner did not provide any instructions or answers to the participant's questions. Shallice and colleagues (1989) suggested that Lhermitte's use of visuo-tactile stimulation with the objects would lead the patients to think that the examiner expected them to show the use of the object, and therefore *induce* the behaviour. They proposed an alternative *incidental* procedure in which the objects were available on the testing table during the whole testing session, but without presentation or reference to them. They argued that this method would not create expectations that the objects should be used. A recent comparison of both methodologies (Besnard et al., 2009) demonstrated that Lhermitte's and Shallice's methods elicited utilization behaviour with the same incidence rate (three out of 20 patients with lesions in the anterior part of the brain referred to as frontal patients; and 0 out of 20 normal controls).

In the present study, the investigation of utilization behaviour took place in the context of a broader neuropsychological examination. The examiner presented six different sets of utilitarian objects separately at pre-determined times during the testing session. Each set of objects was placed on the testing desk between the participant and examiner, clearly within the participant's field of vision and also in a position that would be within easy reach by the subject. The objects were removed after 30 seconds. The examiner gave no instructions, maintained her gaze fixed on the participant's hands and did not answer if the participant asked a question. As in the Shallice (1989) procedure, the objects were only presented visually. However, they were placed in front of and within the reach of the participants; the objects were not just sitting on the desk, as was the

case in the Shallice procedure. There was no tactile stimulation of the hand with the objects. At a different time during the examination, the grasping reflex was tested by palmar stimulation with the examiner's hand and a pen.

Six different sets of objects were used: a bowl with two fruits; a carafe filled with water and an empty glass; a pen and a sheet of paper; sunglasses; a small box; and an envelope and a sheet of paper. During the 30 seconds of object presentation, the participants' behaviour in relation to the objects was noted. Each action observed with one or more objects was classified either as 'toying' or as 'utilization behaviour'. All participants were evaluated by the same examiner, who was aware of the participants' group; we acknowledge that "blind" and independent scoring of videotaped sessions, as in Shallice et al (1989), would have been optimal.

'Toying' was defined by Shallice and colleagues (1989) as the manipulation of an object without using it in a purposeful way (e.g. picking up a pen). In contrast, 'utilization behaviour' occurs when two objects are used in combination for the purpose for which they were designed (e.g. picking up a pen and using it to write on the paper), as defined by Lhermitte (1983). This definition of utilization behaviour corresponds to Shallice's concept of 'coherent activity'. If two objects of the same set were picked up separately (e.g., picking up the pen, putting it back, and picking up the paper), they were considered as two separate 'toying' instances.

Results

Only two patients displayed utilization behaviour. One patient with prefrontal cortex lesion (F025) grasped the carafe and glass, poured water into the glass and drank. One patient with temporal lobe damage (T020) picked up the pen and scribbled on the sheet of paper. In addition, one healthy control participant (C036) demonstrated behaviour that might be described as "utilization behaviour" with material that was not used for this test. She picked up a tissue on the desk behind the examiner, used it to wipe the laptop screen and threw it into the garbage can. We considered this participant's behaviour an example of utilization behaviour.

Patient F025 had undergone excision of a Grade III glioblastoma in the left dorsal frontal region, extending both medially and laterally. In addition, the anterior part of the body of corpus callosum, involved in the transfer of motor and premotor information, was removed (Fig. 1).

The patient with temporal lobe lesions (T020) who exhibited one instance of utilization behaviour, in addition to three instances of toying, had undergone a right-sided transcortical selective amygdalo-hippocampectomy for the relief of epilepsy. The control participant (C036) who showed utilization behaviour was a neurologically intact female in her sixties with a university degree, no health problems and not taking any psychoactive drugs. There were no signs of cognitive deterioration in the neuropsychological tests: she had a Wechsler IQ higher than 120 and high average to above average memory and attention, as measured by the Digit Span, Logical Memory and Faces subtests of the Wechsler Memory Scale –

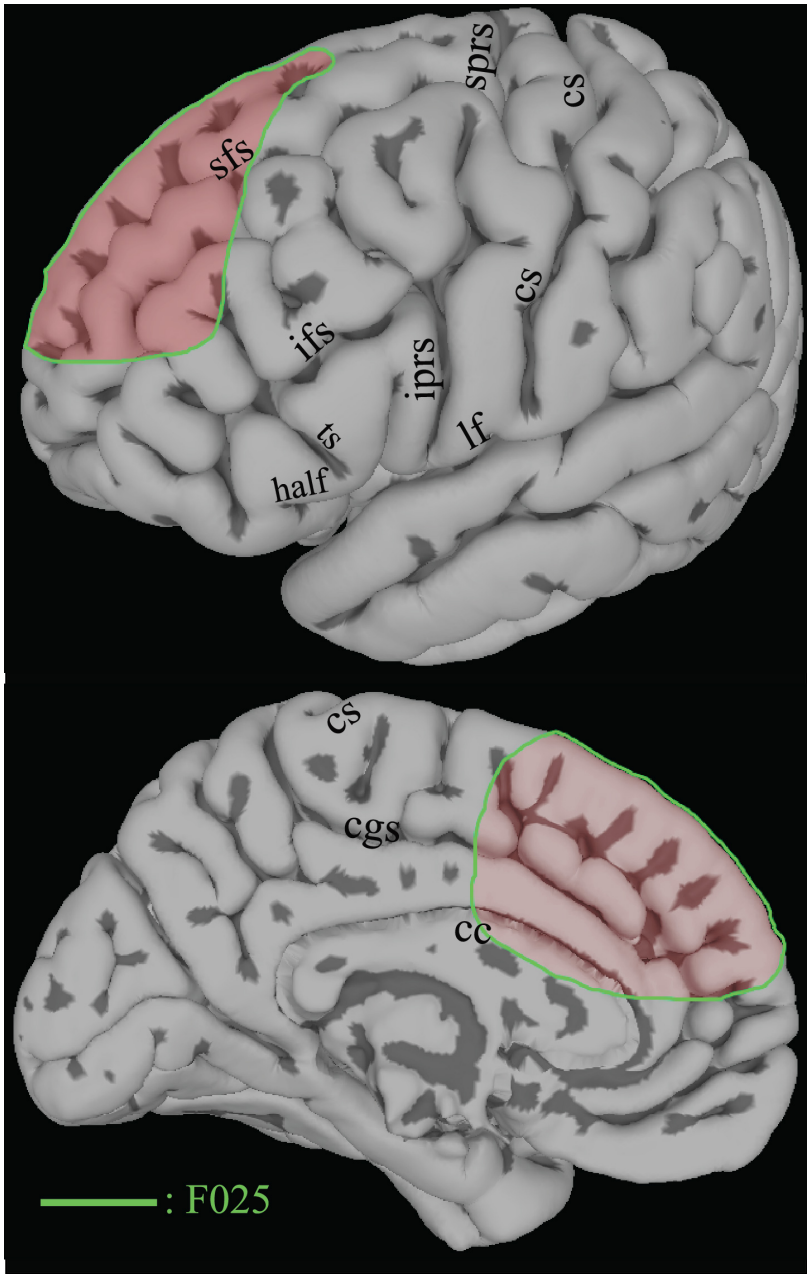
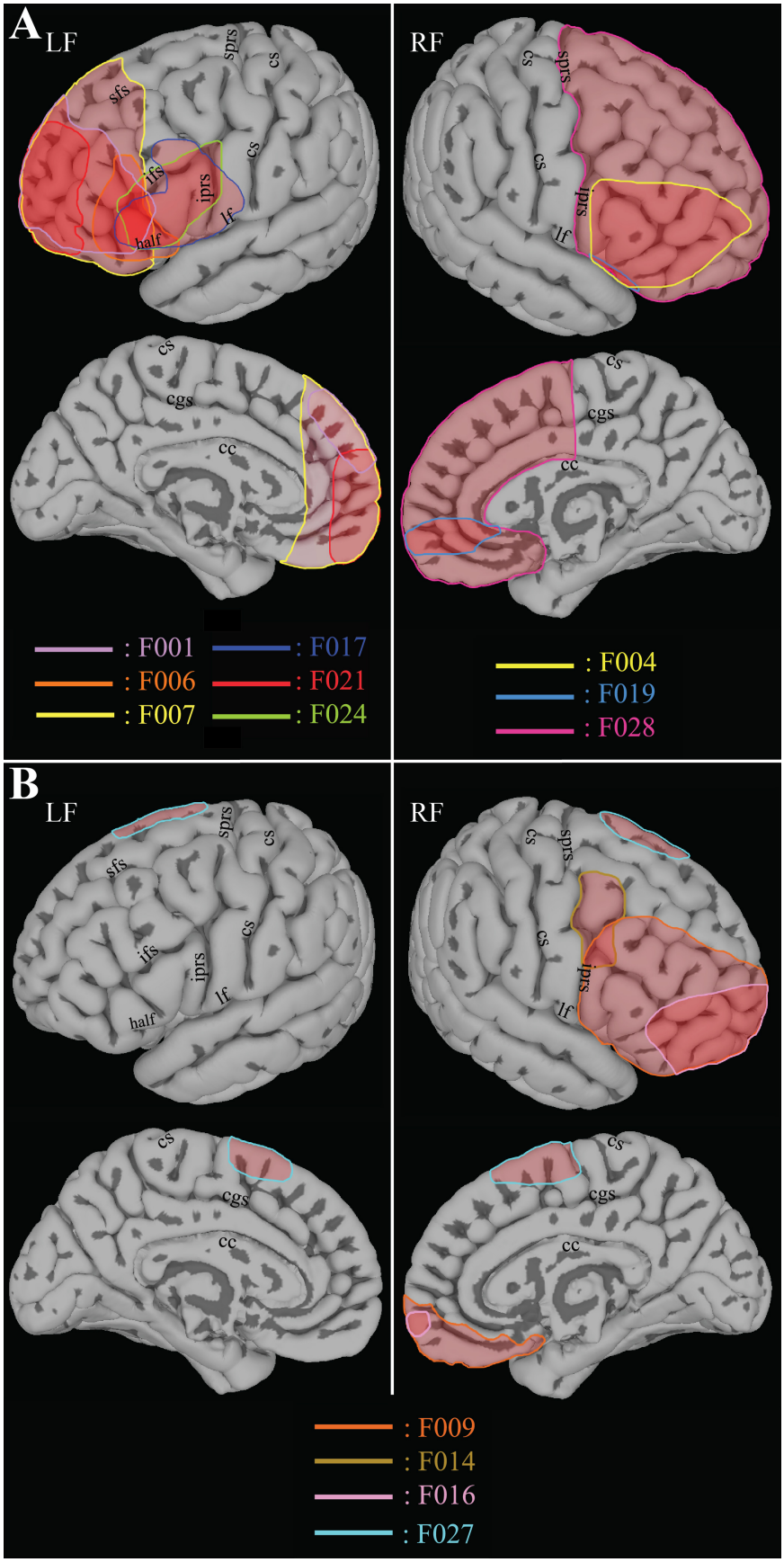


Figure 1. Lesion of the patient (F025) with prefrontal cortex lesions who showed utilization behaviour, displayed on the lateral and medial views of the standard MNI brain Abbreviations: cc, corpus callosum; cgs, cingulate sulcus; cs, central sulcus; half, horizontal anterior ramus of the lateral fissure; ifs, inferior frontal sulcus; iprs, inferior precentral sulcus; lf, lateral fissure; sfs, superior frontal sulcus; sprs, superior precentral sulcus; ts, triangular sulcus.

third edition (WMS-III) and the second edition of the California Verbal Learning Test (CVLT-II).

Although utilization behaviour was rare in both the frontal and the temporal patients, there were many instances of toying across all groups. Thirteen patients out of 20 (65%) in the frontal group toyed with the objects. Figure 2 shows the location of the frontal lesions for patients who exhibited either one or more instances of toying behaviour (A), or no action with the objects (B). Note that the anatomical data was available for only 13 out of 19 of these patients. Eight patients out of 16 (50%) in the temporal group and 8 healthy control participants out of 20 (40%) showed at least one instance of toying during the test. The difference between the three groups in the proportion of participants showing toying in at least one instance did not reach significance according to the chi-square test of independence (χ^2 (2) = 2.532, P = 0.282). A Kruskal-Wallis rank test comparing the sum of toying instances for each participant between the three groups also indicated no significant differences [H (2, N = 56) = 0.926, P = 0.629]. Table 2 shows the proportion of participants from each group displaying overall toying, as well toying for each of the six sets of objects.

In most studies, patients who exhibited utilization behaviour did so with more than one presented object or across situations. In contrast, the three participants demonstrating utilization behaviour in this study displayed it in only one instance and did not appear to demonstrate this behaviour in their everyday life. Moreover, toying was elicited in only one instance in most participants in the present study. That is, 20 out of the 29 participants (69%) with toying behaviour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: F027

Figure 2. The overlap of the individual lesions displayed on the lateral and medial views of the standard MNI brain for 13 patients with left, right and bilateral prefrontal cortex lesions who showed at least one (A) or no (B) instance of toying. Unfortunately, the anatomical data for the remaining six patients with frontal lesions (F015, F020, F022, F023, F026 and F029) were not available. See Figure 1 for label abbreviations. LF, left frontal; RF, right frontal.

showed it only once. Moreover, out of those 20 single instances of toying, 14 occurred with the pen and paper item (70%). This item is likely the one that is the most congruent with a neuropsychological testing situation (Shallice et al., 1989). Therefore, the single instances of toying with this item could be due to normal expectations about the testing situation. Actually, most participants put the pen back down after a couple of seconds when they noticed that nothing was requested of them. If the toying behaviours with the pen and paper were to be excluded, the incidence would decrease to only 25% in the frontal group, 18.75% in the temporal group and 30% in the control group. The difference between the three groups after the toying behaviours with the pen and paper were excluded was also not significant (χ^2 (2) = 0.600, P = 0.741).

Table 2. Proportion of participants from the frontal, temporal and healthy control groups displaying overall toying and toying for each item.

	Frontal n/20 (%)	Temporal n/16 (%)	Control n/20 (%)
Overall Toying	13 (65%)	8 (50%)	8 (40%)
Item 1: Bowl of fruits	3 (15%)	1 (6.25%)	2 (10%)
Item 2: Water pitcher and glass	1 (5%)	2 (12.5%)	3 (15%)
Item 3: Pen and paper	10 (50%)	6 (37.5%)	5 (25%)
Item 4: Sunglasses	1 (5%)	2 (12.5%)	1 (5%)
Item 5: Box	0	0	1 (5%)
Item 6: Envelope and paper	0	1 (6.25%)	1 (5%)

Finally, stimulation of the participants' palms with the examiner's hand or a pen did not induce any reaction or grasp reflex, except in one patient with a right transcortical selective amygdalo-hippocampectomy (T022). However, many other patients with temporal excisions (i.e., T003, T005, T009, T019 and T020) had

similar lesions, but did not show a grasp reflex to the same stimulation. It therefore seems to be an isolated event without necessarily a neural basis.

Discussion

There was no difference in the presentation, nature or frequency of utilization behaviour between patients with prefrontal cortex lesions and patients with temporal lobe lesions. Moreover, both groups had a pattern of utilization behaviour comparable to that of carefully matched neurologically intact individuals. Only one subject from each group displayed behaviour that might be considered "utilization behaviour", and in only one instance. Furthermore, even patients with extensive frontal cortical lesions covering all or a very large portion of the frontal cortex, such as Patients F007, F009 and F028 (Fig. 2), did not demonstrate utilization behaviour. On the basis of these results, we conclude that utilization behaviour is fairly rare among patients with frontal cortex damage, consistent with De Renzi et al's (1996) earlier findings. By including a control group of patients with damage in another part of the brain, namely the temporal lobe, and a normal control group, we also demonstrate that it is not a specific characteristic of damage limited to the frontal cortex. Specificity of frontal contribution and not just general brain damage effect can only be established by including an appropriate patient control group. It is important to point out that prefrontal cortical lesions sustained by the patients included in this study were not asymptomatic: some of the patients with frontal cortical damage exhibited measurable cognitive impairments on tests sensitive to damage of specific parts of the prefrontal cortex. Those patients with damage invading the dorsomedial

frontal region were impaired on a phonological verbal fluency test (Chapados & Petrides, 2013). Patients with dorsomedial frontal damage and ventrolateral frontal damage were impaired in context retrieval on a short-term memory task (Chapados & Petrides, 2014), and some of the patients were impaired on the Wisconsin Card Sorting Test, but these same patients did not exhibit utilization behaviour. The fact that the same lesions lead to specific cognitive impairments, but not to utilization behaviour, further suggests that utilization behaviour does not emerge from specific prefrontal cortical damage, at least not unilateral frontal cortical damage.

In addition, "toying", which is the incidental manipulation of an object in the immediate testing environment in a non-purposeful way, could not differentiate between patients with frontal cortical lesions, patients with temporal lobe lesions and control participants. The fact that toying was observed in 40% of the healthy controls (38.5% being the toying with the pen and paper) indicates that it is a common and normal behaviour in the present context. It probably reflects partly expectations of participants in the testing situation, absentmindedness, and a way to dissipate nervousness in front of the examiner. In this sense, toying is probably not reflecting brain damage, and not the best way to test utilization behaviour. The inclusion of a well-matched normal control group demonstrated, for the first time, that object toying is a frequent behaviour in a normal group and is not more frequent in patients with either frontal or temporal lobe damage.

Only one patient with prefrontal excision (Patient F025) demonstrated utilization behaviour as defined by Lhermitte (1983) and this was the only case in

which the lesion was a grade III tumour invading the anterior part of the corpus callosum. This case should be interpreted with caution since one temporal patient and one normal control also exhibited utilization behaviour.

The present results are consistent with several earlier studies that emphasized the role of extra-frontal damage, particularly to subcortical structures, such as the basal ganglia, in eliciting utilization behaviour (Laplane et al., 1981; Lhermitte, 1983; Lhermitte et al., 1986; Shallice et al., 1989; Degos et al., 1993; Eslinger et al., 1995; Hashimoto et al., 1995; De Renzi et al., 1996; Rudd et al., 1998; Ishihara et al., 2002; Besnard et al., 2009). Utilization behaviour has also been observed in patients with progressive supranuclear palsy, which involves dysfunction of the frontostriatal system (Ghaki, Tennis, Growdon, Hoffman & Johnson, 1995). Although the present results can be interpreted as being consistent with the suggestion that damage to subcortical structures alone or in combination with frontal cortical damage may be necessary for utilization behaviour, they provide no information about which subcortical structures might be critical since none of the patients investigated in the present study sustained a lesion involving the caudate nucleus, the internal capsule or any parts of the thalamus.

In some cases described by Lhermitte (1983), utilization behaviour was present in the acute phase after the surgery or incident, but eventually disappeared. This, combined with the fact that utilization behaviour was not observed in the present patients who were tested on average ~8 years post-incident, might suggest that utilization behaviour is a transient phenomenon. Unfortunately, most single-case reports of utilization behaviour (e.g., Laplane et

al., 1981; Shallice et al., 1989; Eslinger et al., 1995; De Renzi et al., 1996; Ishihara et al., 2002) only tested utilization behaviour in the acute phase, but did not provide information about the long-term presence of utilization behaviour. However, there are reports of utilization behaviour that persisted for months (Brazzelli et al., 1994; Brazzelli & Spinnler, 1998; Boccardi et al., 2002) and even years (Rudd et al., 1998; Balani et al., 2009; Besnard et al., 2009) after the incident, or that presented in the context of neurodegenerative diseases (e.g., Ghaki et al., 1995; Besnard et al., 2009). These cases of long-lasting utilization behaviour showed large bilateral and diffuse lesions extending outside the frontal cortex (e.g., Brazzelli et al., 1994; Brazzelli & Spinnler, 1998; Boccardi et al., 2002; Balani et al., 2009; Besnard et al., 2009) or damage to the striatum, especially the caudate nucleus (e.g., Ghaki et al., 1995; Rudd et al., 1998). Thus, it is possible that the transient utilization behaviour observed in previous studies (e.g., Lhermitte, 1983) was caused by some short-term physiological effects of the incident or surgery, such as inflammatory processes and swelling, on *surrounding* brain areas. The region that was affected acutely while the patients displayed utilization behaviour might have been larger and encompassed even more regions outside the frontal cortex than what was reported. When those global effects eventually resolved, utilization behaviour disappeared. In contrast, in cases of extensive and diffuse damage not restricted to the frontal cortex, utilization behaviour appears to be long-lasting. Although the present study did not investigate utilization behaviour during the immediate post-operative period or post-incident period in the case of cerebrovascular accident, the patients were examined over a wide range of post-operative or post-incident times, ranging

from 11 months to 50 years. Regardless of the length of time since the brain damage, the patients with frontal lesions did not exhibit utilization behaviour, except for one patient who was examined 6.58 years postoperatively.

Archibald and colleagues (2001) proposed a pathophysiological mechanism of utilization behaviour involving dysfunction of the medial motor system structures, including the supplementary motor area and the cingulate gyrus, as well as the basal ganglia, the anterior and medial thalamus, and their interconnections. The medial motor system is assumed to exert inhibitory control over the lateral motor system, which is comprised of the parietal cortex, the cerebellum and the lateral thalamus and whose role is the initiation of exploratory, approach and utilization behaviours based on environmental cues. The results of the present study would not be inconsistent with this suggestion of such a motor circuit, but clearly indicate that lesions restricted to the medial frontal motor structures are not sufficient to elicit utilization behaviour.

The present findings emphasize the importance of basing claims about frontal cortical function on lesions restricted to the frontal cortex and no more than the immediately subjacent white matter. The rather loose use of the term 'frontal lobe' to describe lesions that involve anterior brain damage that may include parts of the frontal cortex but invades extensively subcortical structures (e.g. caudate nucleus) has resulted in mis-attribution of impairments to the prefrontal cortex. It is becoming clear from the present results and other recent studies (e.g., Reitan & Wolfson, 1995; Carey et al., 2008; Possin et al., 2009; Heflin et al., 2011; Chapados & Petrides, 2013) that damage restricted to the frontal cortex is not sufficient to cause impairment on several so-called 'frontal'

executive functions and that damage outside the frontal cortex may have been, either in isolation or in combination with frontal cortical dysfunction, the cause of these impairments.

Connecting text – Study 2 to Study 3

In addition to previous claims that the frontal cortex is the seat of general executive functions that can be measured by the Frontal Assessment Battery (Dubois et al., 2000) or displayed in utilization behaviours (Lhermitte, 1983), there are also claims in the frontal literature that damage to the frontal cortex results in impairment of memory for the context of an event (e.g., Shimamura & Squire, 1987; Duarte et al., 2005). Utilization behaviours can be considered as contextually inappropriate motor behaviours resulting from strong object-action associations without consideration to the context in which the action with the presented object takes place. However, Study 2 demonstrated that damage restricted to the frontal cortex did not result in the exhibition of contextless utilization behaviour. Similarly, Thaiss & Petrides (2003, 2008) found that frontal cortex lesions did not lead to impairments of memory for context. One might ask whether the frontal cortex may play a role in context memory only under certain circumstances.

It is often argued that instead of having a direct role in memory, the frontal cortex contributes to memory in an indirect fashion by controlling different strategic processes critical for memory retrieval under particular circumstances (e.g., Moscovitch, 1992; Incisa della Rocchetta & Milner, 1993; Petrides, 2002, 2005). There is now considerable functional neuroimaging evidence suggesting that the ventrolateral prefrontal cortex is involved in the retrieval of information when the relations between the stimuli and their contexts are unstable and when top-down controlled processes are required to disambiguate between the different pieces of information (Cadoret et al., 2001; Kostopoulos et al., 2007; Kostopoulos

& Petrides, 2003, 2008). However, as is well known, functional neuroimaging evidence is correlative and only lesion studies can establish a causal link and provide unambiguous evidence with regard to the necessary role of a part of the brain in a particular aspect of cognitive processing. This is possible with the carefully selected patients studied in this thesis and whose lesions were well documented. In Study 3, we investigated whether patients with frontal lesions involving the ventrolateral cortex were impaired on such disambiguation processing on a context retrieval task with words and backgrounds.

In addition, because Study 1 provided indications that the left dorsomedial prefrontal region might also be involved in verbal retrieval we explored the role of this region in mnemonic context retrieval. In Study 1, we found that the phonological verbal fluency (mental flexibility) subtest of the Frontal Assessment Battery (Dubois et al., 2000) was sensitive to damage restricted to the left dorsomedial frontal cortex (Chapados & Petrides, 2013). Among other processes, verbal fluency requires the retrieval from memory of specific pieces of information under particular parameters. While the left dorsomedial region may contribute to verbal fluency through its role in energization (Stuss & Alexander, 2007) or in the initiation and emission of intentional speech (Chapados & Petrides, 2013), it may also play a role in verbal memory retrieval under certain circumstances. Therefore, the roles of both the ventrolateral and left dorsomedial regions of the prefrontal cortex were investigated in mnemonic context retrieval in the following study.

Study 3

Ventrolateral and Dorsomedial Prefrontal Cortex Involvement in Mnemonic Context Retrieval

Catherine Chapados and Michael Petrides

This work has been submitted for publication.

Abstract

The prefrontal cortex appears to contribute to the mnemonic retrieval of the context within which stimuli are experienced but only under certain conditions, which remain to be clarified. Patients with lesions to the frontal cortex, the temporal lobe, and neurologically intact individuals were tested for context memory retrieval when verbal stimuli (words) had been experienced across multiple contexts (unstable context condition) or in unique contexts (stable context condition); basic recognition memory of these words-in-contexts was also tested. Patients with lesions to the right ventrolateral prefrontal cortex were impaired on context retrieval *only* when the words had been seen in multiple contexts, demonstrating that this prefrontal region is critical for active retrieval processing necessary to disambiguate memory items embedded across multiple contexts. Patients with lesions to the left dorsomedial prefrontal region were impaired on both context retrieval conditions, regardless of the stability of the stimulus-to-context associations. Conversely, prefrontal lesions sparing the ventrolateral and dorsomedial regions did not impair context retrieval. Only patients with temporal lobe excisions were impaired on basic recognition memory. The results demonstrate a basic contribution of the left dorsomedial frontal region to mnemonic context retrieval, with the ventrolateral prefrontal cortex engaged, selectively, when contextual relations are unstable and require disambiguation.

Introduction

There is consensus on the essential involvement of medial temporal lobe structures, such as the hippocampus and parahippocampal cortex, in various aspects of declarative memory, including context retrieval (Scoville & Milner, 1957; Smith & Milner, 1981, 1989; Nadel & Moscovitch, 2001; Eichenbaum et al., 2007). By contrast, the contribution of the frontal cortex in mnemonic context retrieval remains a matter of debate. There is functional neuroimaging and electrophysiological evidence for greater prefrontal cortex activation during the retrieval of the contextual information associated with an event compared with retrieval of the event itself (e.g., Dobbins et al., 2002; Fujii et al., 2004; review by Mitchell & Johnson, 2009). Similarly, impairment in memory for source (i.e. context) but not for item has been reported following large frontal lesions (Shimamura & Squire, 1987; Janowsky et al., 1989; Shimamura et al., 1990; Duarte et al., 2005), suggesting a critical role of the prefrontal cortex in context retrieval. However, source memory impairments have not always been reported in patients with lesions clearly *restricted* to the prefrontal cortex (Thaiss & Petrides, 2003, 2008), raising the question of the precise conditions under which context retrieval depends on different parts of the large and anatomically heterogeneous prefrontal cortex.

It is often argued that the contribution of the prefrontal cortex in memory is indirect in the sense that it reflects various control processes that may be critical for memory retrieval under particular circumstances (Petrides, 2002, 2005; Moscovitch, 1992; Stuss & Alexander, 2005; Badre & Wagner, 2007).

Specifically, it has been argued that the ventrolateral prefrontal region (areas 45 and 47/12) is critical for active controlled retrieval that would become increasingly important when stimuli are linked to multiple contexts with more or less equal probability creating ambiguous relations between items and their contexts (Petrides, 2002, 2005). By contrast, the ventrolateral prefrontal region would not be necessary for mnemonic context retrieval that can be based on strong and stable stimulus-to-context relations (Petrides, 2002, 2005). Thus, the engagement of the prefrontal cortex in context/source retrieval is not obligatory and the ventrolateral prefrontal cortex becomes necessary as ambiguity in item-to-context relations increases. This specific hypothesis was tested with functional neuroimaging and evidence was provided for selective increases in activity in the ventrolateral prefrontal cortex when human subjects were retrieving specific stimulus features that had occurred in association with multiple contexts (Cadoret et al., 2001; Kostopoulos et al., 2007; Kostopoulos & Petrides, 2003, 2008), but direct evidence of the critical involvement of an area in such retrieval, which can only be provided by lesion studies, is not available.

There is, however, evidence that lesions that involve the ventrolateral region of the frontal cortex in the left hemisphere impair the retrieval of semantic information under conditions of high selection competition demands (Thompson-Schill, D'Esposito, Aguirre & Farah, 1997; Robinson, Blair & Cipolotti, 1998; Jefferies & Lambon Ralph, 2006). There is also functional neuroimaging evidence of the involvement of the left ventrolateral prefrontal region in verbal recall under conditions that require selective verbal retrieval, such as the free recall of words that appeared within particular contexts (lists) (Petrides, Alivisatos & Evans,

1995) and verbal fluency, which can be viewed as a form of selective verbal retrieval (Phelps, Hyder, Blamire & Shulman, 1997; Amunts et al., 2004; Robinson et al., 2012). Another frontal region that has been implicated in verbal fluency is the left dorsomedial prefrontal region (Robinson et al., 2012; Stuss et al., 1998; Chapados & Petrides, 2013), raising the question whether this region may also be involved in the retrieval of stimulus-to-context relations.

The present study tested the above predictions by examining the performance of patients with damage to the frontal cortex on three memory retrieval conditions in which the level of ambiguity between stimulus items and their contexts was manipulated by varying the probability with which a stimulus (word) and a context (background) appeared in relation to one another (Kostopoulos & Petrides, 2003, 2008). Performance of patients with lesions to the frontal cortex was compared with that of patients with temporal lobe lesions that had involved the hippocampus and parahippocampal cortex, as well as healthy control subjects. It was predicted that patients with lesions invading the ventrolateral prefrontal region would perform normally in context retrieval if stimuli and their contexts were stably associated with each other, but that these patients would be impaired if stimuli were linked to multiple contexts and, thus, requiring top-down control to retrieve the relevant stimulus-to-context links.

Materials and Methods

Subjects

Patients. Forty-three patients with circumscribed brain lesions were included in the study and divided into two groups: 23 patients with lesions in the

frontal cortex and 20 patients with lesions in the temporal lobe. Patients were tested from six months to 26 years and two months after the operation or incident, with an average of 4.00 years (SD = 4.29) for the patients with frontal lesions and 6.89 years (SD = 7.85) for the patients with temporal lesions. The frontal and temporal groups did not differ in terms of time elapsed since surgery [t (41) = 1.523, p = 0.136]. None of the patients had comorbid neurological or psychiatric disorders.

Frontal Group. Patients included in the frontal group had damage restricted to the frontal cortex and no more than the immediately subjacent white matter. It consisted of 13 patients with lesions in the left hemisphere, nine in the right hemisphere and one with a small bilateral frontal cortical excision of a tumor in the supplementary motor area. Among the 13 patients with left-sided frontal lesions, 11 had undergone neurosurgery for the resection of a tumor and one for the removal of epileptogenic tissue, and one of them had a stroke. All surgical removals spared the precentral motor cortex, except for one patient (Patient F005). The patient with a stroke (Patient F024) sustained damage in Broca's region in the left hemisphere, but was free of aphasic symptoms at the time of testing.

Six of the nine patients in the right frontal group had undergone resection of a cerebral tumor and two of epileptogenic tissue; one patient had a stroke. The left- and right-sided frontal lesions are shown in Figures 1 and 2, respectively. The anatomical data were not available for four patients (F015, F022, F023 and F029), but we had confirmation from the neurosurgeon that the lesions were

restricted to the frontal cortex. Patient F023 had a left-sided lesion whereas patients F015, F022 and F029 had right-sided lesions. The operation report for patient F015 specifies that she underwent a corticectomy of the mid-SMA on the medial aspect of the superior frontal gyrus, extending 4 cm in the rostral-caudal axis and 2.5 cm in the dorsal-ventral axis.

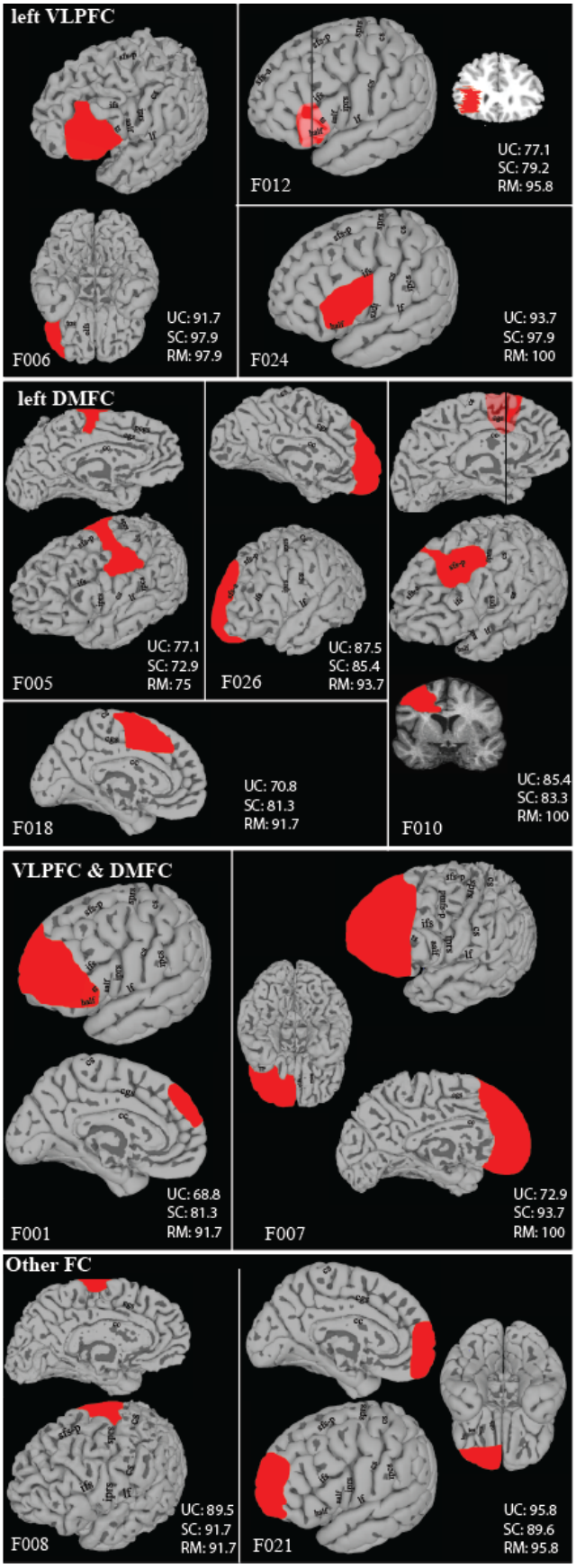

left VLPFC
F006
UC: 91.7
SC: 97.9
RM: 97.9
F012
UC: 77.1
SC: 79.2
RM: 95.8
F024
UC: 93.7
SC: 97.9
RM: 100
left DMFC
F005
UC: 77.1
SC: 72.9
RM: 75
F026
UC: 87.5
SC: 85.4
RM: 93.7
F018
UC: 70.8
SC: 81.3
RM: 91.7
F010
UC: 85.4
SC: 83.3
RM: 100
VLPFC & DMFC
F001
UC: 68.8
SC: 81.3
RM: 91.7
F007
UC: 72.9
SC: 93.7
RM: 100
Other FC
F008
UC: 89.5
SC: 91.7
RM: 91.7
F021
UC: 95.8
SC: 89.6
RM: 95.8

Figure 1. The cortical extent (in red) of lesions in the frontal lobe in the left hemisphere. The medial, lateral, ventral and coronal extents of the lesions are shown when relevant. The lesions are displayed on the 3D reconstruction of the postoperative MRI for Patients F005, F006, F007, F008, F010 and F026; and on the standard Montreal Neurological Institute (MNI) brain for Patients F001, F012, F018, F021 and F024. In the latter cases, tracings of the lesions were used with MRIcro software (Rorden & Brett, 2000) to display them on the MNI brain. The lesions were divided according to whether they included the ventrolateral prefrontal cortex (left VLPFC), the left dorsomedial frontal region (left DMFC), both the VLPFC and DMFC (VLPFC & DMFC), or spared both regions (Other FC). The anatomical data were not available for Patient F023. The scores in percent correct for the three memory retrieval conditions are indicated at the right of each lesion.

Abbreviations: aalf, ascending anterior ramus of the lateral fissure; cc, corpus callosum; cgs, cingulate sulcus; cs, central sulcus; DMFC, dorsomedial frontal cortex; FC, frontal cortex; half, horizontal anterior ramus of the lateral fissure; ifs, inferior frontal sulcus; ipcs, inferior post-central sulcus; iprs, inferior precentral sulcus; lf, lateral fissure; los, lateral orbital sulcus; mos, medial orbital sulcus; olfs, olfactory sulcus; pcgs, paracingulate sulcus; pmfs-p, posterior middle frontal sulcus – posterior; RM, recognition memory condition; SC, stable context retrieval condition; sfs-a, superior frontal sulcus – anterior; sfs-p, superior frontal sulcus – posterior; sprs, superior precentral sulcus; tos, transverse orbital sulcus; TP, temporal pole; ts, triangular sulcus; UC, unstable context retrieval condition; VLPFC, ventrolateral prefrontal cortex.

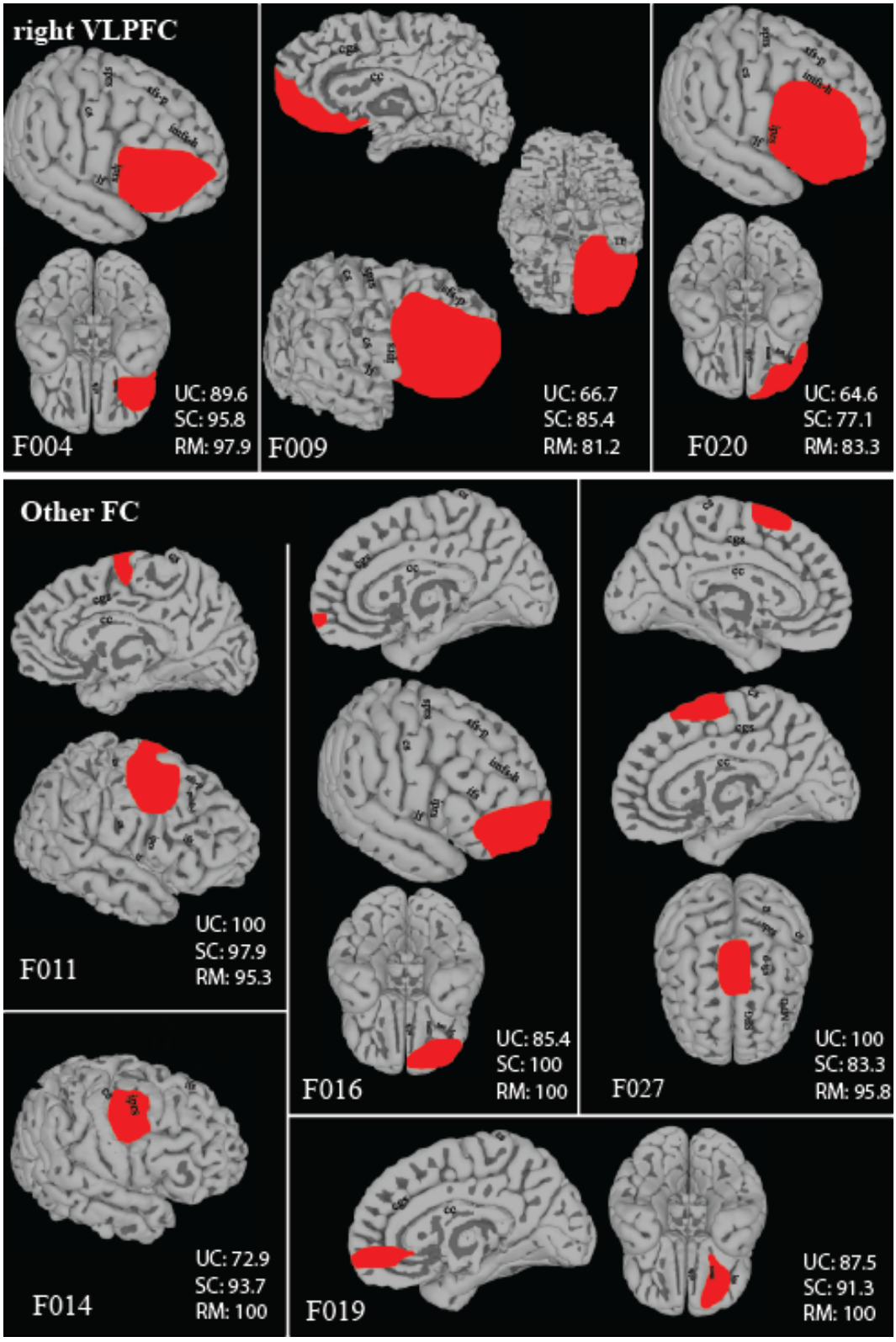

right VLPFC
F004
UC: 89.6
SC: 95.8
RM: 97.9
F009
UC: 66.7
SC: 85.4
RM: 81.2
F020
UC: 64.6
SC: 77.1
RM: 83.3
Other FC
F011
UC: 100
SC: 97.9
RM: 95.3
F016
UC: 85.4
SC: 100
RM: 100
F027
UC: 100
SC: 83.3
RM: 95.8
F014
UC: 72.9
SC: 93.7
RM: 100
F019
UC: 87.5
SC: 91.3
RM: 100

Figure 2. The cortical extent (in red) of lesions in the frontal lobe in the right hemisphere and of the bilateral lesion. The medial, lateral, ventral and dorsal extents of the lesions are shown when relevant. The lesions are displayed on the 3D reconstruction of the postoperative MRI for Patients F009, F011 and F014; and on the standard MNI brain for Patients F004, F016, F019, F020 and F027. In the latter cases, tracings of the lesions were used with MRIcro software (Rorden & Brett, 2000) to display them to the MNI brain. The lesions were divided according to whether they included the VLPFC (right VLPFC; top panel) or spared both the VLPFC and the DMFC (Other FC; bottom panel). The anatomical data were not available for Patients F022 and F029. The operation report for Patient F015 specifies that she underwent a corticectomy of the mid-SMA on the medial aspect of the superior frontal gyrus, extending 4 cm in the rostral-caudal axis and 2.5 cm in the dorsal-ventral axis. The scores in percent correct for the three memory retrieval conditions are indicated at the right of each lesion.

Abbreviations: imfs-h, intermediate middle frontal sulcus – horizontal; MFG, middle frontal gyrus; pmfs-i, posterior middle frontal sulcus – intermediate; SFG, superior frontal gyrus. See Fig 1 for remaining abbreviations.

Temporal Group. This group comprised 12 patients with left-sided lesions and eight with right-sided lesions. The left temporal group included three patients who had surgery for the relief of epilepsy, eight who had tumor resection, and one who had a stroke. The three surgical removals of epileptogenic tissue consisted of either a selective amygdalo-hippocampectomy (n = 2) in which these two structures are resected with the surrounding cortex, or an anterior temporal lobectomy (n = 1) that also included the amygdala and the anterior part of the hippocampus. Of the eight tumor resections, two were standard anterior temporal lobectomies. Three tumor patients underwent selective amygdalo-hippocampectomy, with the additional excision of the middle temporal gyrus in one case. One tumor resection involved the posterior third of the inferior temporal gyrus, with slight extension on the middle temporal gyrus and the white matter underlying the cortical excision. The anatomical data for the remaining two temporal tumor excisions and for the only patient with a stroke were not available, but there was confirmation from the neurosurgeon or neurologist that the lesions were restricted to the temporal lobe.

The right temporal group included five patients with removal of epileptogenic tissue (4 selective amygdalo-hippocampectomies and one anterior temporal lobectomy) and three patients with tumor removal whose anatomical data were not available.

Healthy control participants. Twenty-three healthy control subjects were also included. They were neurologically intact individuals with no history of traumatic brain injury or any neurological or psychiatric disorder. They were matched as closely as possible with the two patient groups for age and education.

Only participants (patients and healthy subjects) with a full-scale Wechsler IQ score above 79 were included in the study. There was no significant difference between the three groups for mean age [F (2, 63) = 0.342, p = 0.711], years of education [F (2, 63) = 0.284, p = 0.753] and IQ [F (2, 61) = 1.200, p = 0.308]. All patients and participants were right-handed, with the exception of two left-handed patients with frontal lesions (Patients F015 and F018), one ambidextrous patient with temporal lesion (Patient T003) and two left-handed control participants. Characteristics of the participant groups are presented in Table 1.

Table 1. Characteristics of participant groups

Group	**Gender**		**Age**	**Education**	**Time since surgery (years)**	**Wechsler IQ**
	M	F	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Frontal	7	16	48.83 (9.47)	15.48 (3.33)	4.00 (4.29)	110.41 (13.76)
Left	5	8	46.85 (9.88)	15.69 (3.30)	2.99 (3.52)	112.08 (10.73)
Right	2	7	51.11 (9.20)	14.78 (3.46)	4.58 (4.71)	106.38 (18.19)
Bilateral	0	1	54 -	19 -	11.92 -	121 -
Temporal	13	7	46.75 (11.34)	14.85 (2.37)	6.89 (7.85)	107.00 (11.55)
Left	8	4	44.42 (11.70)	15.5 (2.24)	5.69 (6.36)	107.73 (13.52)
Right	5	3	50.25 (10.50)	13.88 (2.36)	8.68 (9.88)	106.00 (8.93)
Control	8	15	49.35 (11.44)	15.39 (2.92)	- -	113.04 (12.22)

Experimental Design

The logic of the experimental design was as follows. Individual words (i.e. items) were to be presented on particular unique colored rectangles (i.e. contexts). Participants were required to recall the words in their contexts. There were three retrieval conditions. In the control *recognition memory condition*, a series of these words-in-contexts were to be presented and, later, during memory testing, the subjects would be required to recognize these words in their contexts (targets) from new words in new contexts (distracters).

This basic control memory recognition condition provides the background against which to assess specific memory retrieval of the context in which words had been experienced. It was expected that lateral frontal lesions, unlike medial temporal lobe lesions, would not impair basic recognition memory. Two context memory retrieval conditions were designed in order to test the specific hypothesis that the ventrolateral prefrontal region is not necessary to retrieve the context of items if the items and their contexts are strongly associated with each other (e.g. unique item-to-context relations), but it becomes critical if the items and their contexts are not strongly associated with each other as is the case when items have been experienced under multiple contexts with equal frequency. In the *stable context retrieval condition*, subjects experienced words in unique contexts (as in the control condition), but in the *unstable context retrieval condition* words were experienced under multiple backgrounds with equal frequency and thus there were no strong item-to-context associations to support retrieval of the context of a word from memory.

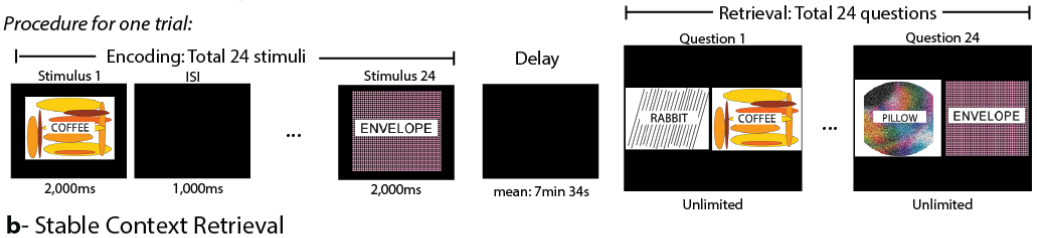
Since the basic recognition memory control condition would be expected to be the easiest one, pilot research was carried out with normal subjects to increase its difficulty to levels comparable to those of the two context retrieval conditions by increasing the delay between the presentation of the stimuli and memory testing. Based on this pilot research, a delay of approximately 7 min in the recognition memory condition was determined to lead to a level of performance comparable to that of the other two retrieval conditions in which the delays were within the 2 to 4.5 sec range. Thus, the difficulty of the control recognition memory condition emanated primarily from the number of stimuli and the delay between the experience of the events and the memory testing, while that of the context retrieval conditions emanated from the retrieval of the specific context of an event after very short delays.

Experimental Material

The stimuli were words appearing on particular colored backgrounds, i.e. the contexts (Fig 3). A total of 147 words each one appearing in combination with one of 147 backgrounds were used for this experiment. The words were all emotionally neutral nouns balanced for frequency and imageability. The mean word frequency count (Kucera & Francis, 1967) was 44.59 (SD: 47.60) for the recognition memory condition, 31.05 (SD: 33.77) for the stable context retrieval condition, and 42.83 (SD: 56.64) for the unstable context retrieval condition [$F(2,144) = 1.143$, $p = 0.323$). The mean imageability rating (Pavio, Yuille & Madigan, 1968) was 586.17 (SD: 14.92) for the recognition memory condition, 592.95 (SD: 26.40) for the stable context retrieval condition, and 586.00 (SD:

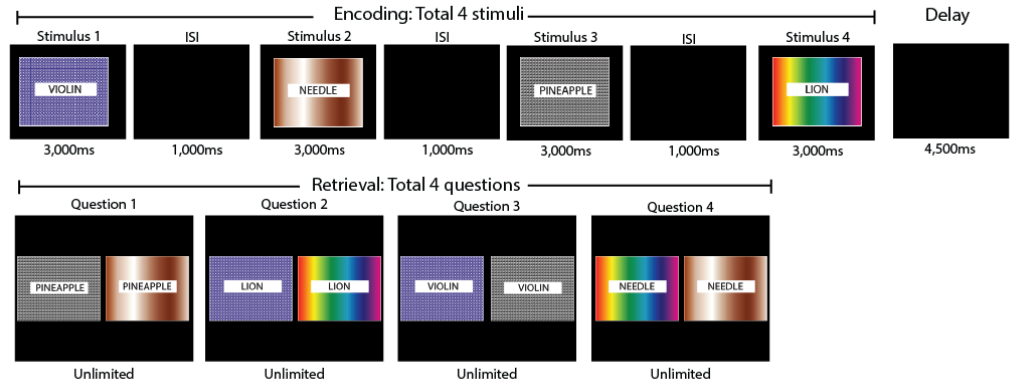
a- Recognition Memory

Procedure for one trial:



b- Stable Context Retrieval

Procedure for one trial:



c- Unstable Context Retrieval

Nine possible stimulus-complexes

Procedure for one trial:

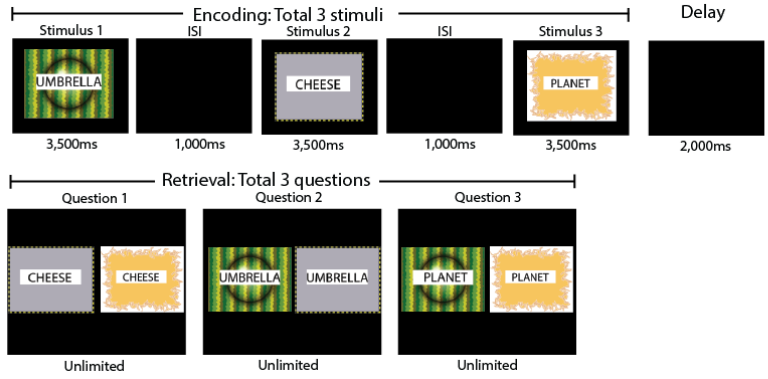


Figure 3. Schematic diagram of the testing procedure of the recognition memory condition (A), the stable context retrieval condition (B), and unstable context retrieval condition (C). Note that the size of the screen for the encoding and retrieval phases was exactly the same in the experiment. However, in order to make the words legible in the retrieval phase of the illustration, the screen is enlarged and the question is removed. Abbreviation: ISI: inter-stimulus interval.

27.63) for the unstable context retrieval condition [F (2,144) = 0.780, p = 0.461]. The words were written in black in 72-point Arial font on a white background and each word was placed in the center of a colored 15 cm by 10 cm rectangular context. These contexts were abstract nonverbal colored designs created for the purpose of this experiment using Adobe® Illustrator® and Photoshop®. It was shown that semantic similarity, even between picture and words (Lupker & Katz, 1981), exerts an interfering influence for retrieval, as concepts compete with one another (Damian, Vigliocco & Levelt, 2001). Because we wanted no pre-existing relationships, thus no potential conceptual interference, between words and backgrounds in order to manipulate experimentally the level of ambiguity between them, neutral abstract backgrounds were used. These word-in-context stimuli were presented on a laptop computer screen with E-prime® (Psychology software Tools, Inc.), a specialized psychology program for stimulus presentation and data collection.

Procedure

Testing on the experiment was preceded by a practice session during which instructions were presented on the screen and read to the participants, with examples of the stimuli. The subjects completed a few practice trials before the beginning of the testing session in order to familiarize themselves with the task and to make sure they understood and could perform it properly.

Each condition comprised different trials all of which included an encoding phase, a delay, and a retrieval testing phase (Fig 3). The testing session started with the encoding phase of the *recognition memory condition*. Twenty-four word-in-context stimuli were presented in a random order for 2,000 ms each

with an interstimulus interval of 1,000 ms. Patients were instructed to memorize these stimuli. When all 24 word-in-context stimuli had been presented, a long delay of ~7 min (Mean: 7 min 34 sec, SD: 47 sec) was interposed between the presentation of the stimuli (encoding phase) and the presentation of the testing stimuli (retrieval testing phase). During this long delay, half of the trials from the stable and unstable context retrieval conditions were administered (see below).

During the retrieval testing phase of the recognition memory condition, participants saw pairs of word-in-context stimuli on the screen, one on the left and one on the right (Fig. 3A). One of the stimuli had been presented in the encoding phase (target) and the other was a new word in a new context, a stimulus that the participant never saw before (distracter). Thus, there were 24 such pairs, one for each one of the 24 stimuli presented during the encoding phase. The left-right position of the target and distracter was randomly determined but in a balanced manner so that the target and the distracter appeared an equal number of times on the left and right sides. The following question was presented at the top of the screen: "*Which of these two words did you see previously?*" Participants were instructed to select the stimulus they had seen during the encoding phase in a forced-choice paradigm by pressing on the appropriate key ("1" for the stimulus on the left or "0" for the stimulus on the right) on the laptop keyboard. There was no limit on the time to respond. For the item recognition condition, there were two trials, each one consisting of the presentation of 24 word-in-context stimuli. Thus, a total of 48 stimuli were presented for encoding and 48 pairs of stimuli (target and distracter) for retrieval.

In the *stable context retrieval condition*, there were 12 trials, each one consisting of the presentation of four word-in-context stimuli during the encoding phase and of four pairs of testing stimuli during the retrieval phase, for a total of 48 encoding stimuli and 48 pairs of testing stimuli (Fig 3B). During the encoding phase of each trial, four word-in-context stimuli were presented one at a time, each one for 3,000 ms with an interstimulus interval of 1,000 ms. In this condition, participants were instructed to remember the association between each word and the context in which it had appeared. After a delay of 4,500 ms, four pairs of testing stimuli were administered, one for each of the four stimuli just presented. The target was one combination of word and context presented during the encoding phase and the distracter was the same target word, but presented on a context associated with another word during the encoding phase. Thus, all four contexts served as distracter for another word in the same trial (see Fig 3B). Two stimuli were presented below the question ("*On which background was this word presented?*") and participants had to select the target context.

In the *unstable context retrieval condition*, only three words and three contexts were used and the word-in-context stimuli presented during the different trials were the nine possible combinations of these three words and three colored contexts (Fig. 3C). In the encoding phase of each trial, each one of the three words was presented once and in one of the three contexts, i.e. three of the nine possible combinations of the 3 words and 3 contexts were presented. Each stimulus was presented for 3,500 ms with an interstimulus interval of 1000 ms. A delay of 2,000 ms was interposed between the encoding phase and the retrieval phase, which consisted of the presentation of three pairs of testing stimuli. Each

pair consisted of one of the three word-in-context stimuli presented during encoding (target) together with the same target word but on one of the other two contexts (distracter). Recall that in this condition only three words and three colored contexts were used and the words and contexts were combined randomly but equiprobably across the whole experiment. During the retrieval phase, the following question was presented: "*The last time you saw this word, on which background was it presented?*" with two stimulus-complexes below the question. Sixteen trials were administered, each trial presenting three word-in-context stimuli during encoding and three testing pairs, for a total of 48 stimulus-complexes for encoding and 48 pairs of stimulus-complexes during memory testing.

The experimenter ensured the participants understood what they had to memorize during the encoding phase (i.e. the word on the particular context background) and on what basis they had to respond during the testing phase (i.e. the targets were the words presented on the correct context backgrounds for that particular trial) in the unstable and stable context retrieval conditions).

Results

A three group (frontal, temporal, and healthy controls) by three retrieval conditions (unstable context retrieval, stable context retrieval, and recognition memory) repeated measures ANOVA was carried out to examine group differences on memory retrieval performance. Figure 4 shows the mean retrieval performance in percent correct responses for each group across the three retrieval conditions. The ANOVA yielded a significant interaction between participant

group and retrieval condition [F (4, 126) = 3.147, p = 0.017; F (3.5, 110) = 3.147, p = 0.022 with adjusted degrees of freedom using the Greenhouse-Geisser estimate of sphericity **(**Epsilon 0.8758). Each group was then compared with the healthy control group within each memory condition using the Dunnett test. In the recognition memory condition, the patients with temporal lesions performed significantly worse than healthy controls (p = 0.033). There was no difference in performance between the normal control subjects and the frontal group (p = 0.997) in the recognition memory condition. It is important to note that only in this condition was the delay between the encoding phase and the recognition test longer than a few seconds (~7min). Thus, the temporal lesions created sensitivity to delay, but the frontal lesions did not. In the stable context retrieval condition, the temporal group was impaired in comparison with the control group (p = 0.057), but the frontal group was not impaired (p = 0.1160). In the unstable context retrieval condition, there was a trend for an impairment in the group of patients with frontal cortical lesions in comparison with the healthy control subjects (p = 0.060). Because this difference was a predicted one, we also report the result of the Fisher LSD test: p = 0.033. The patients with temporal lesions did not differ from controls on the unstable context retrieval condition (p = 0.547).

Note that the performance of the patients with temporal lesions was comparable across the three retrieval conditions and the absence of significant impairment in the temporal group on the unstable retrieval condition may have been due to the lower performance of the control subjects on this condition, thus decreasing the difference between control and the temporal group rather than to an absence of impairment *per se* in the temporal group. However, we must also

note that only three stimuli were shown during the presentation phase in the unstable condition and the memory testing took place only 2 sec later. Patients with temporal lesions perform well on short-term memory tasks that do not exceed their normal span (Scoville & Milner, 1957; Smith & Milner, 1981, 1989). Even the severely amnesic patient HM with bilateral medial temporal lobe lesions had no deficit with very short delays (Scoville & Milner, 1957).

In the temporal group, the effect of laterality of the lesions was also examined by comparing patients with left- and right-sided temporal lesions within each retrieval condition. Independent sample t-tests yielded no significant difference for the stable context retrieval [t (18) = 0.097, p = 0.924] and the recognition memory [t (18) = -0.283, p = 0.780] conditions. In the unstable context retrieval condition, there was a trend for the patients with right temporal lesions to perform worse than patients with left temporal lesions [t (18) = 1.799, p = 0.089].

Figure 4.

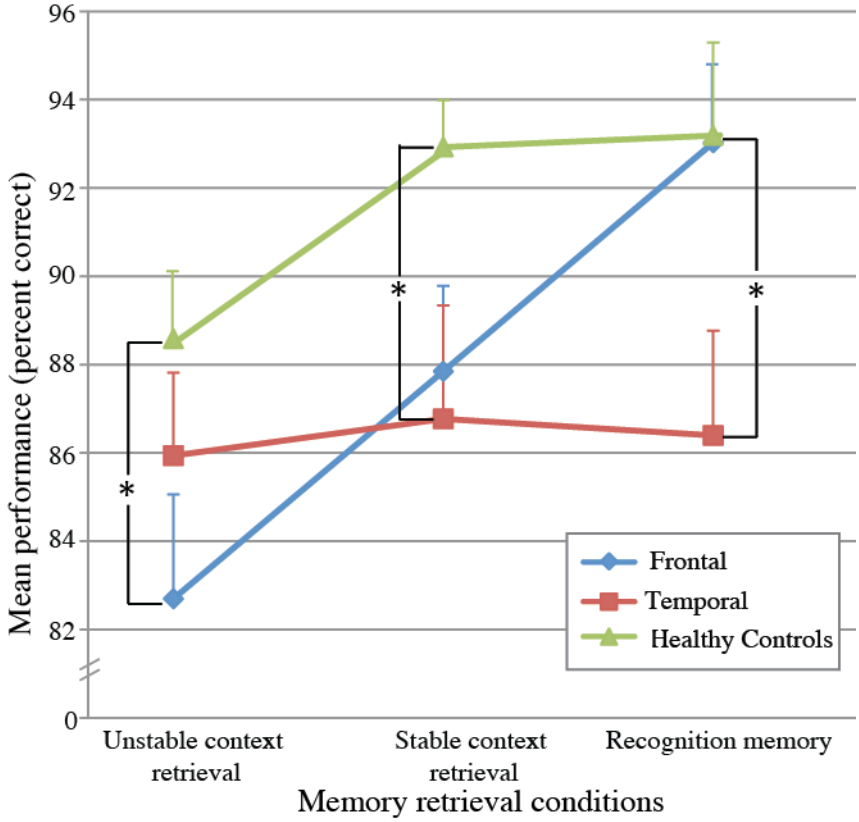


Figure 4. Graph showing the mean performance of each group across the three memory retrieval conditions. Error bars represent the standard error. * $p < 0.05$

In the preliminary analysis reported above, the patients with lesions anywhere in the frontal cortex were treated as a single group so as to examine overall differences between the effects of frontal and temporal lesions. However, the experiment was designed to test the specific prediction that the ventrolateral prefrontal cortex (VLPFC) may be critical for the disambiguation of mnemonic traces when the relations between stimuli and their contexts are unstable (Cadoret et al., 2001; Kostopoulos et al., 2007; Kostopoulos & Petrides, 2003, 2008). The

unstable context retrieval condition was designed specifically to test the above hypothesis that patients with lesions to the VLPFC would be selectively impaired on this condition which assesses active controlled retrieval. In addition, we had previously shown that lesions invading the left dorsomedial region of the frontal cortex (DMFC) yield impairment in verbal fluency (Chapados & Petrides, 2013). One fundamental requirement in verbal fluency tasks is the retrieval from verbal long-term memory of words that meet certain requirements. Thus, the verbal fluency deficit after left DMFC lesions may be reflecting a more general retrieval impairment.

In a second series of analyses, we examined the above specific predictions within the frontal group. Patients with frontal cortical lesions were divided into the following sub-groups: 1) patients with lesions invading only the left VLPFC (left VLPFC; n=3); 2) patients with lesions invading only the right VLPFC (right VLPFC; n=3); 3) patients with only left DMFC lesions (left DMFC; n=4); 4) patients with damage to the frontal cortex that did not invade either the VLPFC or the left DMFC (Other FC; n=8). Patients included in the Other FC subgroup had lesions that did not invade the mid-ventrolateral prefrontal cortex (cytoarchitectonic areas 45 and 47/12 as defined by Petrides & Pandya (2002) and, therefore, no VLPFC). In addition, these lesions had to spare the dorsomedial frontal cortex that in Chapados & Petrides (2013) reduced verbal fluency: the dorsomedial frontal cortex anterior to the supplementary motor area (SMA), including the pre-SMA, the cingulate motor areas, and medial areas 8, 9 and 32 (thus no DMFC). Note that no patient had lesion to the right dorsomedial frontal region analogous to the one found to be critical for verbal fluency. In addition,

two patients with lesions that invaded both the left VLPFC and the left DMFC could not be assigned to either group. Their performance is discussed individually below. The three patients with frontal lesions whose anatomical data were not available were not included in this analysis. The mean scores on each retrieval condition for the four frontal sub-groups and the control group are presented in Figure 5.

To test the specific predictions about the individual frontal sub-groups, one-way ANOVAs were conducted to compare the five groups (left VLPFC, right VLPFC, left DMFC, Other FC, and healthy control) for each one of the three retrieval conditions, followed by the Dunnett test. Significant differences were found in the unstable [$F(4,36) = 3.226$, $p = 0.023$] and stable [$F(4,36) = 4.309$, $p = 0.006$] context retrieval conditions, but not in the item recognition condition [$F(4,36) = 1.026$, $p = 0.407$]. Only the right ventrolateral prefrontal group was impaired on the unstable context retrieval condition in comparison with the control subjects ($p = 0.009758$, one-tailed; 0.019505, two-tailed). Although the left DMFC group was not significantly impaired relative to the control group according to the Dunnett test, the difference was significant with the Fisher LSD ($p = 0.0497$ uncorrected).

In contrast, on the stable context retrieval condition, only patients with left dorsomedial frontal cortex lesions were impaired in comparison with the healthy control subjects ($p = 0.019$, one tailed; 0.037, two-tailed). The patients with frontal lesions sparing both the VLPFC and the left DMFC performed like normal subjects on all three memory conditions (Fig 5).

The performance of the right VLPFC group was significantly lower on the unstable context retrieval condition in comparison with both the stable ($p = 0.017$) and the recognition memory ($p = 0.014$) conditions, but there was no significant difference in the performance of this group between the stable context and recognition memory conditions ($p = 0.939$) (Newman-Keuls multiple comparisons test). In addition, on the unstable context retrieval condition, the right VLPFC group was impaired in comparison with the Other FC group ($p = 0.034$) and marginally with the left VLPFC group ($p = 0.060$) (Newman-Keuls multiple comparisons test). There was no difference in the performance of the left VLPFC group between the three memory retrieval conditions.

Thus, the essential finding was that lesions limited to the right VLPFC impaired performance only on the unstable context retrieval condition, as predicted. The left DMFC lesions clearly impaired performance on the stable context retrieval condition and also on the unstable context retrieval condition (based on planned comparison).

Finally, the scores of the two patients whose prefrontal lesions included both the left VLPFC and DMFC were low on the unstable context retrieval condition (68.75 and 72.92). On the stable context retrieval condition, one patient's performance (81.25) was similar to that of the left DMFC only group, whereas the other patient (93.75) performed like the other groups. These double-lesion patients strengthen the argument that the left DMFC and perhaps also the left VLPFC play a role in the contextual retrieval of information.

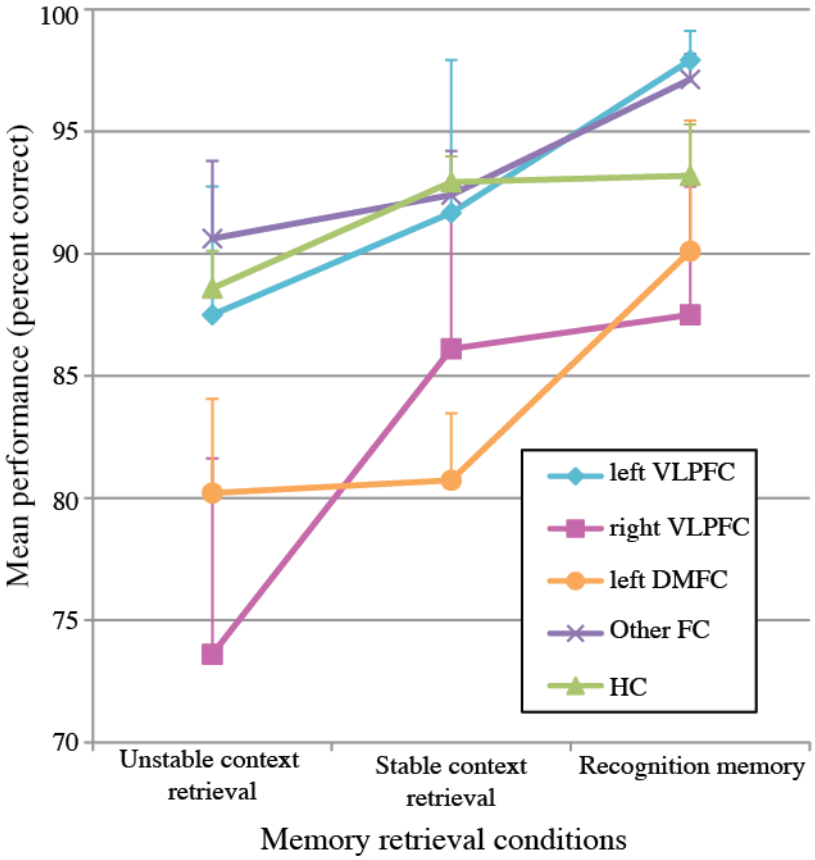


Figure 5. Graph showing the mean performance on the three memory retrieval conditions of the four frontal groups: patients with lesions 1) including the left ventrolateral prefrontal cortex (left VLPFC), 2) including the right ventrolateral prefrontal cortex (right VLPFC), 3) including the left dorsomedial frontal cortex (left DMFC), 4) sparing both the VLPFC and left DMFC (Other FC); and of normal control subjects (HC). Error bars represent the standard error.

Discussion

In the present experiment, patients with frontal and temporal lesions were tested on three memory conditions that required retrieval of items and their contexts. In the control condition, subjects could perform well on the basis of

mnemonic recognition of the previously experienced word-in-context stimuli. In both the stable and unstable context retrieval conditions, however, subjects had to retrieve explicitly the context associated with the words. The difference between the latter two conditions was the fact that, in the stable context condition, each word had been seen in only one context (unique and stable relations between items and contexts), while in the unstable context condition the words had been seen in all the contexts across trials (multiple relations of items and contexts). The first major finding of the present study was a clear dissociation between the effects of lesions to the frontal cortex and those to the temporal lobe for basic recognition memory retrieval. In the recognition memory condition, the patients with temporal lesions performed significantly worse than the healthy controls, but the patients with frontal lesions performed as well as the control subjects. The difficulty in the recognition memory task emanates from the relatively large number of stimuli presented (24 stimuli vs. 4 and 3 in the two context retrieval conditions) and the relatively long delay between stimulus presentation and memory testing (7 min vs. a few seconds in the context retrieval conditions). These results are consistent with the well-established fact that the hippocampus and related structures in the medial temporal lobe are essential for item memory (Scoville & Milner, 1957; Mishkin, 1982; Squire & Zola-Morgan, 1991; Nadel & Moscovitch, 2001; Bachevalier & Nemanic, 2008). The normal performance of patients with frontal cortical lesions on the recognition memory condition confirms previous research that patients and monkeys with lesions of the lateral frontal cortex are not impaired on basic recognition memory (Bachevalier & Mishkin, 1986; Petrides, 1995, 2000a,b).

In sharp contrast to their normal recognition memory with a relatively long list of stimuli (24 stimuli) and long delay (~7min), patients with lesions that invaded the right ventrolateral prefrontal region were impaired selectively on the unstable context retrieval condition despite the low number of stimuli presented during the encoding phase (3 stimuli) and the very short delays between stimulus presentation and memory testing (2 sec). Here it is important to note that patients with frontal cortical lesions that spared the ventrolateral prefrontal region and the left dorsomedial verbal fluency retrieval region (Chapados & Petrides, 2013) were not impaired on either of the two context retrieval conditions, emphasizing the regional specificity of frontal cortical impairments. Thus, consistent with the hypothesis tested in the present experiment, the patients who had lesions that included the right ventrolateral prefrontal cortex were impaired on the context memory retrieval task in which stimulus-to-context relations were unstable, but were not impaired when these relations were stable (Fig 5).

The lack of impairment in the left ventrolateral prefrontal group may have been due to the fact the lesion of one patient in this group was not complete with area 47/12 clearly spared (see Patient F024 in Fig 1). Alternatively, there may be a difference between the right and left ventrolateral prefrontal regions that remains to be explored further. For instance, the three words in the unstable context retrieval condition were not entering into variable relations with other words or semantic contexts, but rather abstract visual backgrounds and this may have been the major source of ambiguity in the unstable context retrieval condition. Thus, the abstract visual contexts may have created a source of ambiguity that was demanding more processing from the right hemisphere as far

as context disambiguation was concerned and, of course, the right hemisphere is dominant for the processing of abstract stimulus material (Milner, 1971). This argument receives some support from the fact that patients with right temporal lesions tended to perform slightly worse than those with left temporal lesions on this condition.

The present results provide the first cause-and-effect confirmation of the essential role of the ventrolateral prefrontal cortex in active retrieval processing necessary to disambiguate items and their context in memory, which had previously received support from neuroimaging studies (Petrides, 2002; Cadoret et al., 2001; Kostopoulos et al., 2007; Kostopoulos & Petrides, 2003, 2008). Petrides (2002, 2005) argued that the ventrolateral prefrontal cortical region (areas 45 and 47/12) may be a critical part of the prefrontal cortex for the active controlled retrieval of information in situations in which items of information exist in memory under multiple associations with one another and, therefore, top-down control processing is necessary to disambiguate the memory traces that are assumed to lie in the posterior association neocortex. It is important to note that the normal performance of the patients with ventrolateral prefrontal lesions on the stable context condition demonstrates that these patients can retrieve the context of a word recently experienced and can easily separate this context from other recently experienced contexts that were associated with other recently experienced words. Thus, the impairment on the unstable context condition stems not from a difficulty in discriminating between recent events (recency impairment), but rather from the need to retrieve the *specific* context under which

a stimulus had been experienced on a particular trial when that stimulus had previously been experienced under multiple contexts.

The experimental design of the present study permits a demonstration of the critical role of the right ventrolateral prefrontal cortex in the disambiguation of item-to-context relations in memory when there are no strong unambiguous relations between items and their contexts to enable bottom-up retrieval. The finding that the ventrolateral prefrontal region is critical for selective retrieval under conditions of high selection demands is consistent with demonstrations that the left ventrolateral prefrontal region (inferior frontal gyrus) plays a key role in the control of semantic retrieval (Thompson-Schill et al., 1997; Robinson et al., 1998; Jefferies & Lambon Ralph, 2006), especially when a given stimulus activates the retrieval of many competing verbal response options; it is also consistent with functional neuroimaging evidence of the involvement of the left ventrolateral prefrontal region in demanding verbal recall, such as the free recall of words on particular lists (Petrides et al., 1995) and verbal fluency (Phelps et al., 1997; Amunts et al., 2004).

The design of the present experiment provides some insight into the reason why demanding retrieval may require the ventrolateral prefrontal region. Theoretically, in the unstable context retrieval task, upon the presentation of each word on the test trials, any one of the three competing contexts has an equal chance of being retrieved. Successful retrieval of the required context on a particular trial depends on active disambiguation processing, namely enhancement of the appropriate context and suppression of the other contexts under which the word had also appeared, but on different trials. Single-unit recording in the

macaque ventrolateral prefrontal cortex, i.e. cytoarchitectonic areas 45 and 47/12, provided evidence of neuronal activity that can underlie this disambiguation process which is the basis of active controlled retrieval. After an instruction to retrieve a specific aspect of a memorized complex stimulus (such as its color, but not its shape), a class of neurons in the ventrolateral prefrontal cortex responds selectively to the isolation of the instructed aspect of a memorized stimulus [see Cadoret & Petrides (2007) for details]. Thus, there is evidence of neuronal processing isolating particular aspects of memorized experiences.

Unlike the patients with right ventrolateral prefrontal lesions, the patients with left dorsomedial frontal lesions were clearly impaired on the stable context retrieval condition, and to a lesser extent, on the unstable context retrieval condition. This group had similar performance on both the stable and unstable context retrieval conditions, suggesting a difficulty in retrieving the item-to-context relations, regardless of their stability.

A plausible explanation for the finding that the left dorsomedial frontal cortex is involved in context retrieval comes from the idea that the dorsomedial prefrontal region plays a role in sustained attention, cognitive effort, and 'energization' (Stuss & Alexander, 2007). Energization refers to the process of sustaining a response after initiation. According to this view, the dorsomedial prefrontal region is recruited when a task requires maintaining a specific response over time, or producing new responses that are not overlearned. Energization is considered to be domain-general and could, therefore, also be recruited for memory retrieval tasks. In this sense, context retrieval is less automatic and requires more cognitive effort than basic recognition of an episode or an item,

because a given context must not only be recognized, but also associated with the correct item and dissociated from incorrect items. Energization could thus be needed in order to sustain sufficient activation to complete this type of task. If the contextual information needs to be disambiguated because of unstable context-to-item relationships, the ventrolateral prefrontal cortex would then be additionally recruited. These two regions would play two distinct executive roles at two different levels in context retrieval.

An alternative interpretation may be that the left dorsomedial prefrontal region plays a role in context retrieval in a more direct manner. Poor performance following lesions in this region on both context retrieval conditions could be driven by the basic requirement to retrieve the context within which particular words were embedded. Thus, the present findings could provide evidence, for the first time, that this region which had previously been linked with verbal fluency (Stuss et al., 1998; Robinson et al., 2012; Chapados & Petrides, 2013) is also involved in verbal item-to-context memory retrieval. This is consistent with the idea that the phonological verbal fluency task examines the capacity to retrieve from memory items falling under specific parameters, such as words beginning with a certain letter, to select the appropriate words and to differentiate them from words that do not meet the criteria.

The critical region for verbal fluency found by Chapados and Petrides (2013) in the dorsomedial frontal cortex included the supplementary speech zone, the cingulate motor region, the paracingulate cortex and the medial prefrontal areas 8 and 9. This dorsomedial frontal region, which is linked with the hippocampal/parahippocampal region (Morris, Pandya & Petrides, 1999), may

play a central role in episodic memory retrieval. Temporal lesions impair basic memory (i.e. both item recognition and retrieval of context), reflecting the necessary role of the hippocampus and parahippocampal cortex in forming new memories, such as binding an item with its context (e.g., Smith & Milner, 1981, 1989; Mishkin, 1982; Parkinson, Murray & Mishkin, 1988; Malkova & Mishkin, 2003; Park, Shannon, Biggan & Spann, 2012). By contrast, the impairment after left dorsomedial frontal lesions appears in the context of normal recognition memory as shown by the present findings. Thus, the limbic medial temporal structures are necessary to encode and maintain strong memory representations of the words and their contexts, while the left dorsomedial frontal region contributes to the retrieval of words in their context. For both the temporal and the left dorsomedial frontal lesions, ambiguity of stimulus-to-context relations and the need to disambiguate these relations during memory retrieval was not a critical factor influencing performance. This effect of ambiguity was clearly observed only in patients with right ventrolateral prefrontal lesions. We know that anatomically the ventrolateral prefrontal cortex is linked with the dorsomedial prefrontal region in both the monkey (Petrides & Pandya, 2002) and the human brain (Margulies & Petrides, 2013), although the meaning of these connections had remained unclear until now. This dorsomedial frontal region was also co-activated with the ventrolateral prefrontal region in the functional neuroimaging studies of controlled active memory retrieval [e.g. Kostopoulos & Petrides, 2003, see Fig 2B and Table 1; Kostopoulos & Petrides, 2008, see Fig 2B and 2C and Table 1]. Thus, the present results suggest that the left dorsomedial frontal region is involved in context memory retrieval and its bi-directional link with the

ventrolateral prefrontal region permits engagement of the latter region when the traces in memory are embedded in multiple contexts and, therefore, the relations among stimuli become ambiguous. Based on the present results, one could hypothesize the existence of a circuit comprising the hippocampus and adjacent medial temporal cortex, the dorsomedial region of the frontal cortex and the ventrolateral prefrontal cortex, each playing distinct roles in stimulus-context retrieval in episodic memory.

General Discussion

A significant part of the literature on frontal cortical functions has been built on studies of patients with damage assumed to lie in the frontal cortex. However, many of these patients did not have damage restricted to the frontal cortex, but rather massive damage to the anterior part of the brain. The damage often invaded subcortical structures, such as the basal ganglia, the thalamus and important fiber tracts, as well as extra-frontal cortical regions. It is clearly impossible with this type of patient selection to draw precise conclusions about frontal anatomo-functional relations.

The aim of this thesis was to test some major claims about frontal functions originating from this literature by examining the effects of damage limited to the frontal cortex. One goal of this research was to test the claim that the Frontal Assessment Battery (Dubois et al., 2000) is a sensitive tool to assess frontal executive dysfunctions. The second goal was to test whether frontal cortical damage can give rise to motor behaviour that is contextually inappropriate, as in the proposal by Lhermitte (1983) that frontal lesions result in utilization behaviour. In both cases, the claim is that generalized executive problems follow frontal cortical damage that can be measured by a specific battery of frontal tests, the Frontal Assessment Battery (Dubois et al., 2000), or exhibited in contextually inappropriate behaviour, i.e. utilization behaviour (Lhermitte, 1983). In utilization behaviour, the presented object (e.g., apple) may act as a cue triggering the action strongly associated with the object (e.g., picking up the apple and eating it), but the context (e.g., hospital testing room) is not taken into consideration, resulting in a contextually inappropriate action. Consequently,

the research conducted for this thesis also examined the common claim that context specific memory retrieval depends on the prefrontal cortex (e.g., Duarte et al., 2005; Mitchell & Johnson, 2009). Finally, the present work examined the specific hypothesis that context specific impairments can follow in cognitive situations where memory retrieval depends on active disambiguation emanating from the mid-ventrolateral prefrontal cortex (Petrides, 2002, 2005). The recruitment of this prefrontal region by the need to disambiguate between items (words) and their contexts (coloured backgrounds) was explored by manipulating the stability with which items and contexts entered in relationships with one another in a mnemonic context retrieval task. In addition to examining claims about general executive functions of the frontal cortex existing in the literature (i.e., that global executive impairments, as measured by the Frontal Assessment Battery or exhibited in utilization behaviour, result from frontal damage), this thesis addressed a specific hypothesis about a particular aspect of executive processing (i.e., the control of context retrieval in situations requiring disambiguation), believed to be controlled by a specific region of the frontal cortex, namely the ventrolateral prefrontal cortex. This approach of relating specific cognitive processing and specific cortical regions is believed to be the best way to approach brain-behaviour relationships (e.g., Petrides, 2005; Stuss, 2007; Stuss & Alexander, 2007).

In order to control for the general effects of disease and treatment, the performance of patients with lesions restricted to the frontal cortex was compared with that of patients with lesions in another part of the brain, the temporal lobe.

This approach allowed determining whether specific frontal cortical regions were critically involved in functions commonly claimed to be 'frontal' functions.

Absence of generalized impairments in patients with lesions *restricted* to the frontal cortex

Frontal Assessment Battery. The Frontal Assessment Battery (Dubois et al., 2000) is a commonly used measure intended to assess frontal dysfunction. Unfortunately, this battery was validated on patients with a variety of neurodegenerative conditions causing widespread damage to the brain, and, surprisingly, despite its name was never validated on patients with lesions restricted to the frontal cortex. Except for the verbal fluency (mental flexibility) subtest, the overall performance on this battery and performance on five of its subtests were found not to be sensitive to prefrontal cortex damage. Even though we cannot question the usefulness of this battery to assess deficits in patients with neurodegenerative diseases, its overall power to measure frontal cortical dysfunction is questioned by the normal performance of patients with lesions restricted to the prefrontal cortex.

We reviewed over 148 studies that used the FAB since its original publication. Because of its name implying the assessment of frontal cortical function, it was assumed to capture executive functions of the frontal cortex and used as a tool to measure the level of frontal dysfunctions in different populations. Out of 148 reviewed studies using the FAB, approximately a third of them (n = 48) examined performance of patients with various types of dementias (e.g., Kugo et al., 2007; Yoshida et al., 2009), especially in order to test whether the FAB

could be a good cognitive tool to discriminate between frontotemporal dementia and other type of dementias, such as Alzheimer's disease (e.g., Lipton et al., 2005; Valverde, Limenez-Escrig, Gobernado & Baron, 2009). Many studies of patients with Parkinson's disease (n = 42) used the battery in order to assess the presence of frontal abnormalities or dementia (e.g., Bugalho & Vale, 2011; Cohen et al., 2012; Kaszas et al., 2012). The FAB was also assumed to detect 'frontal' executive functions impairments in patients with various other neurological conditions (n = 32), such as stroke (Mok et al., 2004), idiopathic normal pressure hydrocephalus (Miyoshi et al., 2005; Kanno et al., 2012), progressive supranuclear palsy (Withwell et al., 2011), and amyotrophic lateral sclerosis (Terada, Obi, Miyajima & Mizoguchi, 2010), or in other populations (n = 26), such as elderly individuals (Iavarone et al., 2011), individuals with alcohol dependence (Zago-Gomes & Nakamura-Palacios, 2009), and psychiatric patients (Barbosa et al., 2012).

The results reported in the present thesis seriously question the power of this battery to measure frontal cortical dysfunctions since lesions to the frontal cortex resulted in normal global performance on the FAB. Therefore, impairments found on the FAB, except on the verbal fluency (mental flexibility) subtest, do not appear to be sensitive indicators of dysfunction of the frontal cortex and should be interpreted with caution.

Utilization behaviour. A behavioural disturbance commonly thought to be suggestive of frontal dysfunction is utilization behaviour. It refers to contextually appropriate motor behaviour, such as the grasping and using of objects in front of them although not instructed to do so (Lhermitte, 1983). So far,

there has been only suggestive but not conclusive evidence that the frontal cortex is involved in cognitive processes leading to the inhibition of inappropriate utilization behaviour. This is because patients with utilization behaviour reported in previous group studies and single-case reports had sustained lesions to the anterior part of the brain also invading subcortical structures and fiber tracts. Here, on the basis of examining patients with frontal lesions limited to the cortex, we came to the conclusion that the frontal cortex is not critical in the demonstration of utilization behaviour. It therefore seems that the extra-frontal damage, absent in our patients, but present in the previous studies (e.g., Lhermitte, 1983; Lhermitte et al., 1986; Shallice et al., 1989; De Renzi et al., 1996; Besnard et al., 2009) was in part responsible for the demonstration of utilization behaviour in the previously studied patients. However, even though dysfunction of some anterior subcortical structures, especially the caudate nucleus (Lhermitte, 1983; Shallice et al., 1989; Degos et al., 1993; Ghika et al., 1995; Rudd et al., 1998), have been thought as being involved either alone or in combination in the disinhibition of utilization behaviour (Degos et al., 1993; Ghika et al., 1995), we cannot conclude on the role of those subcortical structures on the basis of this study. It would be interesting to compare our patients with patients with lesions restricted to the caudate nucleus or other subcortical structures in order to identify one or more critical areas to utilization behaviour.

A pathophysiological mechanism of utilization behaviour, involving dysfunction of the medial motor cortical regions, the basal ganglia, the anterior and medial thalamus, and their interconnections, has been proposed (Archibald et al., 2001). Motor areas on the medial frontal cortical surface comprise the

supplementary motor complex as well as the cingulate motor areas (see more detailed description of anatomy and connections in the *General literature review*). In addition to their cytoarchitectonic features (e.g. presence of pyramidal cells) and connectivity patterns with major motor structures, there is also functional evidence that these medial frontal cortical regions are involved in motor functions. First, the supplementary motor complex includes the supplementary motor area (SMA), the supplementary eye field and the pre-SMA, which all seem to be involved in different aspects of motor control (see reviews by Goldberg, 1985 and Nachev et al., 2008). While electrical stimulation of the supplementary eye field evokes saccadic eye movements and eye-head movements, the SMA holds a somatotopic representation of the body whose stimulation elicits limb and orofacial movements as well as vocalizations and disinhibition of voluntary speech ('speech arrest'; Penfield & Welch, 1951). Together, the supplementary motor complex is proposed to be a key structure in the control of voluntary self-initiated actions, including speech, by linking different conditions, such as external cues and internal states, in the initiation and elaboration of movements (Nachev et al., 2008). Second, a recent anatomo-functional study demonstrated the existence along the cingulate and paracingulate sulci of three distinct human motor regions (Amiez & Petrides, 2012). They also appear to be somatotopically-organized and to include regions activated by simple externally induced foot, hand, eye and tongue movements. There have been proposals that they might be related (Amiez & Petrides, 2013) to a slightly more rostral, yet overlapping, cingulate area involved in the analysis of behavioural feedback during trial-and-error exploratory situations (Amiez, Sallet, Procyk & Petrides, 2012).

According to Archibald et al., the medial motor system (medial frontal cortical regions and connected subcortical structures) would exert inhibitory control over the lateral motor system. This lateral motor system consists of the parietal cortex, the cerebellum and the lateral thalamus and would play a role in the initiation of approach and utilization behaviours in response to external cues. The results of Study 2 would not be inconsistent with this theoretical proposition, but clearly indicate that damage limited to the medial frontal cortical motor structures (i.e. supplementary motor complex and cingulate motor regions), at least unilaterally, is not sufficient to cause utilization behaviour. Patients with lesions invading these dorsomedial motor regions did not show more utilization behaviours or meaningless manipulation of the presented objects (i.e., toying) than other patients or healthy subjects. They were, however, not asymptomatic as they were impaired in verbal fluency (Study 1) and context retrieval (Study 3).

General role of the prefrontal cortex in executive functions. In summary, performance on both the FAB and utilization behaviour appears to be independent of frontal cortex damage, despite the general assumption that they reflect frontal dysfunctions. Re-examinations of such assumptions are very important in neuropsychology as they allow one to rectify, or specify, some common claims in the literature that were based on patients whose lesions were not restricted to the region of interest. For example, in the past, careful lesion studies conducted by Hebb (1939; 1945) refuted the then-common view that frontal lobe damage was associated with general deterioration of intelligence. The claims that the FAB and utilization behaviour capture frontal cortical dysfunctions were originally based on patients with frontal, but also additional extensive

subcortical and extrafrontal damage, as shown in the *Issues with original lesion studies* section of the *General literature review*. In this thesis, we could demonstrate that lesions restricted to the frontal cortex do not cause deficits on those aspects of executive functions that are measured by the FAB and impaired in the display of utilization behaviour.

Contributions of specific frontal cortical regions

Involvement of the left dorsomedial frontal region in phonemic verbal fluency. In Study 1, performance of patients with frontal cortical lesions on the Frontal Assessment Battery and on each of its six subtests was examined. It was found that only patients with left frontal lesions invading the dorsomedial cortical region above the anterior cingulate region were impaired on the phonemic verbal fluency (mental flexibility) subtest, but on no other subtests of the battery. This is consistent with other studies showing impairment on phonemic verbal fluency in patients with superior medial frontal damage (Stuss et al., 1998; Robinson et al., 2012). In the present study, the dorsomedial frontal cortex anterior and ventral to the supplementary motor area, including the pre-supplementary motor area and the adjacent ventrally located cingulate motor areas (Amiez & Petrides, 2012) seemed to be the critical region. These somatotopically organized cingulate areas are thought to be involved in high-order control of motor responses and in intentional actions, including speech (Paus et al., 1993; Nachev et al., 2008). Disruptive stimulation of the supplementary motor area (Penfield & Welch, 1951) and of some sites along the cingulate sulcus (Chassagnon, Minotti, Kremer, Hoffmann & Kahane, 2008; Jürgens, 2009) elicits vocalizations and speech arrest.

There are several reports of akinetic mutism or disruption in the initiation of spontaneous speech following medial frontal surgery in this region (Rostomily et al., 1991; Ackermann at al. 1996; Zentner et al., 1996; Krainik et al., 2001; Krainik et al., 2003), and of transcortical motor aphasia, a syndrome characterized by limited spontaneous speech, following infarction in the territory of the left anterior cerebral artery causing damage of the left superior medial frontal cortex (Rubens, 1975; Madseu et al., 1978; Racy et al., 1979; Alexander & Schmitt, 1980; Ross, 1980; Goldberg et al., 1981; Freedman et al., 1984; Ziegler et al., 1997; Pai, 1999). It was also argued by Goldberg (1985) and then Passingham (1993) that the medial frontal cortex, especially the region including and surrounding the supplementary motor area, is involved in internally-driven language and action as opposed to actions that are induced by external cues. This theory has received functional neuroimaging support (e.g., Crosson et al., 2001). After the subjects have provided automatically a few easier and more obvious words, a phonemic verbal fluency task essentially requires an internally guided production of words. Together, these findings suggest that the left dorsomedial frontal regions encompassing the supplementary and cingulate motor areas contribute to the initiation and emission of intentional and internally generated speech, which might be necessary to perform successfully a verbal fluency task.

In addition to its role in intentional action (including speech), the dorsomedial prefrontal cortex could contribute to verbal fluency via other processes. Robinson and colleagues (2012) also found impairment on multiple fluency tasks following damage to the superior medial frontal region. Not only were the patients with such lesions impaired on phonemic and semantic verbal

fluency tasks, they were also impaired in the generation of free and fixed designs, of meaningful and meaningless upper limb movements, and of conventional and un-conventional uses of objects (ideational fluency). They suggested that this region plays a role in sustained attention and a process called 'energization' that is necessary for generating new items in fluency tasks, regardless of the modality. Energization refers to the process of maintaining cognitive effort after initiation when a task requires the production of new responses that are not overlearned and automatic (Stuss & Alexander, 2007). It is also believed to be recruited when one must produce rapid rates of responses and maintain vigilance over time, for example in a counting task (Shallice, Stuss, Alexander, Picton & Derkzen, 2008). In the context of a fluency task, energization might be required to sustain activation necessary for the internally-guided generation of the new non-automatic words for the whole trial duration (i.e., one minute) after the few more obvious words have been automatically provided in the first few seconds.

Together, our findings suggest that phonemic verbal fluency requires specific supramodal processes taking place in the dorsomedial region of the prefrontal cortex, but the exact nature of these processes remains to be clarified.

Role of the ventrolateral prefrontal cortex in active memory retrieval. The ventrolateral prefrontal region (areas 45 and 47/12) has been argued by Petrides (2002, 2005) to play a role in top-down control processes for the retrieval of memory traces lying in posterior cortical areas. This process presumed to emanate from the ventrolateral prefrontal region has been referred to as active controlled retrieval. Well-controlled neuroimaging studies have shown greater activation in this region during the retrieval of different stimulus attributes when

they had been embedded with one another in ambiguous relationships, thus requiring controlled retrieval processes (Cadoret et al., 2001; Kostopoulos et al., 2007; Kostopoulos & Petrides, 2003, 2008). In Study 3, we tested whether patients with lesions invading the ventrolateral prefrontal cortex would be impaired in a context retrieval task when such active processes were necessary. In comparison with patients with frontal lesions sparing the ventrolateral prefrontal region, patients with lesions including this region were impaired in context retrieval when stimulus-to-context relations were unstable or multiple. In contrast, their performance was normal when the stimuli were related to contexts in unique and unambiguous ways and thus when automatic recollection was sufficient for context retrieval. These results suggest that the ventrolateral prefrontal region is critical for retrieval from memory of items and contexts that exist in multiple associations with one another, and therefore requiring disambiguation. The present results are consistent with the theoretical proposal by Petrides and provide the first cause-and-effect confirmation of the essential role of the ventrolateral prefrontal cortex in active memory retrieval, which had yet only been suggested from neuroimaging studies (Cadoret et al., 2001; Kostopoulos et al., 2007; Kostopoulos & Petrides, 2003, 2008). In those studies, the contribution of this cortical region in active memory retrieval was observed in many modalities (e.g., tactile, verbal, visuospatial, auditory) and regardless of the stimulus characteristics that had to be disentangled. In the present study, this top-down process was also recruited to disambiguate items (words) and their contexts (colored backgrounds), indicating that this control processing is domain-general and not bound to a specific modality.

The present results are also consistent with a previous patient study by Smith, Leonard, Crane and Milner (1995) showing sensitivity to interference on a spatial memory task following frontal lobe lesions. The same objects were presented in different locations across trials, similar to the present unstable context retrieval condition in which the same words were presented within different contexts across trials. In the latter study, only the *overall* performance of the frontal group was examined, i.e. there was no division of the frontal cortex in terms of different regions. In the present work, a specific prediction about the role of the ventrolateral prefrontal cortex in the disambiguation during retrieval between items and contexts that were related in multiple ways across trials was tested and confirmed.

With regard to the potential underlying mechanisms, the present results indicate that the need for disambiguation that is controlled by the ventrolateral prefrontal cortex emanates from the unstable relationships between the different stimulus items. All words had appeared in multiple and equiprobable combinations with all contexts across trials, thus giving rise to three contextual memory traces of assumed equal intensity for each word. Theoretically, upon the presentation of one cue (i.e., a word), three contexts had the equiprobable chance of being retrieved. The subjects were then required to retrieve only the context in which this word had appeared on a particular trial and to suppress the other contexts in which the word had also appeared, but on different trials, hence the active disambiguation processing. The automatic retrieval of only one context strongly linked to the word was not possible under this paradigm.

The same type of disambiguation was required when the features of

different stimuli (e.g., the location and color of visual stimuli, or the frequency and duration of vibrotactile stimuli) were manipulated in order to appear in multiple and unstable relationships in previous functional neuroimaging (Cadoret et al., 2001; Kostopoulos et al., 2007; Kostopoulos & Petrides, 2003, 2008) and neurophysiological (Cadoret & Petrides, 2007) studies. Single-unit recording in the macaque mid-ventrolateral prefrontal cortex, corresponding cytoarchitectonically to areas 45 and 47/12 of the human brain, provided evidence that neuronal activity of this region underlie disambiguation during active controlled retrieval (Cadoret & Petrides, 2007). During active retrieval, the monkey had to isolate selectively a stimulus component (e.g., color or shape) of a stored memory representation and decide whether it matched this specific component on a test stimulus. It is important to note that all the possible combinations of stimulus components had an equal chance of being presented during testing. This single-neuron recording study identified neurons in the mid-ventrolateral prefrontal cortex firing during different phases of active retrieval: during the cue presentation when the particular to-be-retrieved aspect of the stimulus compound was instructed, during the delay when the active retrieval of the instructed information occurred, and during the test when the cognitive decision that the instructed aspect of the memorized stimulus corresponded had indeed been successfully carried out. The cue-related neurons had differential firing rates depending on the aspect of the stimulus compound that had to be retrieved (e.g., color vs. shape), suggesting that the role of those neurons was to highlight selectively this stimulus aspect (e.g., color), but not the other (e.g., shape), in the memory representations, so it could be matched to this aspect of the

test stimulus when it appeared after the delay. By shifting the attention to only one component of stimuli, this process helped resolve the ambiguity caused by the multiple relationships existing between the different stimulus components that were stored in posterior cortical areas.

In conclusion, the findings of the present patient lesions study along with functional neuroimaging and nonhuman primate electrophysiological studies provide converging powerful evidence that the ventrolateral prefrontal cortex is critical for disambiguation of memory traces during active memory retrieval.

Role of the left dorsomedial frontal region in context retrieval. The left dorsomedial region found to be critical for verbal fluency was also found to play an essential role in context retrieval. Patients with lesions invading this region were impaired at retrieving the context in which they had seen a particular stimulus item, regardless of whether the contexts and items had appeared in unique/strong or multiple/unstable relationships. However, patients with lesions to the left dorsomedial frontal cortex were not impaired in the basic recognition memory of previously encoded items-in-contexts from among new items-in-contexts, in sharp contrast with patients with temporal lobe lesions who were impaired on both recognition memory and context retrieval tasks and whose performance is discussed below.

In a previous patient lesion study by Smith and Milner (1984), patients with frontal lobe lesions were, overall, not impaired in memory for the spatial location of objects, which can be regarded as comparable to the present unique stable context retrieval condition. These findings are consistent with the present findings of no impairment on stable context retrieval for the frontal group as a

whole. Only when examining specifically the performance of patients with lesions invading the dorsomedial frontal cortex, impairment on items-in-contexts memory retrieval was found; note that in the Smith & Milner (1984) object-to-place memory study, any specific contribution of the dorsal medial frontal damage was not explored.

The involvement of the dorsomedial frontal region in memory retrieval is consistent with previous functional neuroimaging studies, which found co-activation of this dorsomedial frontal region along with the ventrolateral prefrontal region during active memory retrieval (e.g. Kostopoulos & Petrides, 2003, 2008). These findings suggest that the dorsomedial frontal region contributes to mnemonic retrieval under certain circumstances, such as when the item of information to be retrieved has to be linked with a particular stimulus, or stimulus feature. This region receives input from the hippocampus and related parahippocampal region (Morris et al., 1999), in accordance with its potential role in retrieval of context from memory.

The involvement of the dorsomedial frontal cortex in context retrieval could also explain how this region contributes to verbal fluency, that is, by controlling the retrieval from memory of items falling under specific parameters, such as words beginning with a certain letter. In this case, the appropriate words have to be selected and differentiated from words that do not meet the criteria. Because the discarded words might share similar attributes, such as the same beginning phoneme, similar sources, or be linked in a certain way in the mental lexicon with the correct words, top-down retrieval processes might be required.

Conclusions. The present findings on context retrieval also partially contribute to a resolution of an existing controversy with regards to the critical role of the frontal cortex in source memory. While some investigators argued that lesions to the frontal cortex result in source memory impairments (e.g., Shimamura & Squire, 1987; Janowsky et al., 1989; Shimamura et al., 1990; Schacter, 1995; Duarte et al., 2005), others did not find such impairments in patients with lesions restricted to the frontal cortex (Thaiss & Petrides, 2003, 2008). The present results suggest a more nuanced and precise view of the role of the prefrontal cortex in source memory: some specific regions of the prefrontal cortex are critical for aspects of the control of context retrieval under specific circumstances. On the one hand, the ventrolateral prefrontal cortex was necessary to isolate particular contexts only when they were embedded with multiple word stimuli in an ambiguous fashion. On the other hand, the left dorsomedial frontal region appeared to be generally involved in the control of memory retrieval when the information to be retrieved was linked to other pieces of information in memory. In the context retrieval tasks, it was recruited when contexts associated with particular words had to be retrieved. In the verbal fluency task, this region was necessary in retrieving words sharing one specific feature (e.g., first letter).

In addition, the fact that only context retrieval, but not basic *recognition* retrieval, was impaired in patients with frontal cortical damage also confirms previous research in patients and monkeys that lesions of the lateral frontal cortex do not impair basic recognition memory (e.g., Bachevalier & Mishkin, 1986; Petrides, 1995, 2000b).

Finally, the observed specific roles of the dorsomedial and ventrolateral frontal cortical regions further contribute to the view that frontal cortical areas serve a diversity of discrete, yet supra-modal, executive functions (e.g., Petrides, 2005; Stuss & Alexander, 2007), rather than being parts of an undifferentiated central executive system or fluid intelligence (e.g., Duncan & Miller, 2002; Roca et al., 2010, 2013).

Contributions of the temporal lobe

Another important finding of the present thesis was the demonstration of a dissociation between the frontal cortex and the temporal lobe in their involvement in basic recognition memory retrieval. When the temporal lobe was damaged, encoding and maintenance of properly encoded material into long-term memory seemed to be more difficult as shown by their impaired performance on the recognition memory condition when the delay between the encoding of information and its retrieval was the longest (about 7 minutes). However, recognition memory was performed at normal levels by patients with frontal cortical lesions. This dissociation is somewhat similar to the dissociation between the middorsolateral prefrontal cortex and the inferotemporal cortex for the manipulation and maintenance of information in visual working memory found by Petrides (2000b) in the nonhuman primates. The present results are also consistent with the well-established fact that the hippocampus and adjacent structures in the medial temporal lobe are essential for item memory (Scoville & Milner, 1957; Mishkin, 1982; Squire & Zola-Morgan, 1991; Nadel & Moscovitch, 2001; Bachevalier & Nemanic, 2008).

In addition, it was found that performance of patients with temporal lobe lesions was similar across the three different retrieval conditions (i.e. recognition memory, stable context retrieval and unstable context retrieval; see Study 3, Fig. 4, p. 113). It suggests that in addition to their critical role in maintaining representations in memory (e.g., Scoville & Milner, 1957; Nadel & Moscovitch, 2001), temporal lobe structures are also involved in forming new associative memories, such as binding an item with a place, in accordance with several hippocampal lesions studies in the rodents, nonhuman primates and human patients (e.g., Smith & Milner, 1981, 1989; Mishkin, 1982; Morris, Garrud, Rawlins & O'Keefe, 1982; Parkinson et al., 1988; Malkova & Mishkin, 2003; Eichenbaum et al., 2007; Park et al., 2012). For instance, it was found that lesions to the right mesial temporal lobe, especially in the presence of extensive damage to the hippocampal formation, caused impairment in the delayed recall of the spatial location of objects (Smith & Milner, 1981, 1984, 1989). In these studies, objects were associated to specific places in unique relationships. This paradigm may be compared to the present stable object-to-context retrieval condition in which patients with temporal lobe damage were also impaired.

In Study 3, the effect of ambiguity in the relationships between items and contexts was not observed in patients with temporal lesions, that is, they performed similarly on the unstable and stable context retrieval conditions. It suggests that the temporal lobe structures are critical for the formation of new item-to-context associations in memory, regardless of their level of ambiguity. This is consistent with the study of Smith et al (1995) in which heightened sensitivity to proactive interference in a spatial memory task was observed only in

patients with frontal lobe damage, but not in patients with temporal lobe damage, thus suggesting that the frontal lobe, but not the temporal lobe, is involved in resolving this interference during retrieval of spatial location.

Clinical implications

The work presented in this thesis has clinical implications. First and foremost, a battery long assumed to be a sensitive measure of frontal cortical function, the Frontal Assessment Battery (Dubois et al., 2000), was shown not to be sensitive to impairments in patients with known frontal cortical damage. In addition, performance on five different subtests assumed to measure different aspects of executive functions controlled by the frontal cortex, such as abstraction, motor planning, resistance to interference, inhibitory control, and environmental autonomy, was normal following lesions limited to the frontal cortex. Furthermore, utilization behaviour, which can be regarded as environmental dependency and context-inappropriate behaviours resulting from poor inhibitory control (e.g., Archibald et al., 2001), was not observed in the present sample of patients with frontal cortical lesions.

Although we do not argue that the frontal cortex is not involved in executive functions, the present findings demonstrate that the way they are measured by the FAB and utilization behaviour do not capture frontal cortical dysfunction. The present findings are thus consistent with the growing literature arguing that some tests of executive functions intended to assess frontal functions are not sensitive to frontal cortex damage (e.g., Reitan & Wolfson, 1995; Stuss & Alexander, 2007; Possin et al., 2009; Heflin et al., 2011; Stuss, 2011; Duffau,

2012; Plaza, du Boullay, Perrault, Chaby & Capelle, 2013), and therefore that 'frontal functions' and 'executive functions' are not necessarily synonymous.

Consequently, the present work underlies the importance of having assessment tools measuring specific aspects of cognitive processing whose underlying mechanisms are well-defined and experimentally controlled, rather than tests assessing general impairments. For instance, the stable and unstable context retrieval conditions of the present context memory tasks are a good example of a specific task that manipulated a specific process (i.e., disambiguation of information in memory) predicted to be controlled by a specific cortical region (i.e., the ventrolateral prefrontal cortex).

There are other instances in the literature of very specific tasks designed to assess one aspect of executive function suspected to be controlled by a particular cortical region, such as the self-ordered pointing task for the mid-dorsolateral prefrontal cortical region (areas 46, 9/46; Petrides & Milner, 1982) and spatial and motor conditional associative learning tasks for more posterior dorsolateral frontal cortex (area 8 and rostral area 6), respectively (Petrides, 1985, 2000a). Results from Study 1 also suggest that the phonemic verbal fluency task is a useful and specific clinical test to detect left frontal dysfunction invading the dorsomedial region, even though the exact nature of the mechanisms underlying verbal fluency remains to be specified. Finally, our findings highlight how crucial it is to validate assessment tools on the appropriate patient and control populations.

Conclusion

In summary, the present thesis provided evidence against two general claims about frontal cortical functions. First, the Frontal Assessment Battery (FAB; Dubois et al., 2000), considered to be a sensitive tool to assess frontal lobe dysfunctions, was shown to be neither sensitive nor specific to lesions restricted to the frontal cortex, except for the verbal fluency (mental flexibility) subtest (Study 1). Second, we also demonstrated that patients with lesions restricted to the frontal cortex do not exhibit more utilization behaviour (Lhermitte, 1983) than individuals with lesions to the temporal lobes or neurologically intact subjects (Study 2).

On the other hand, some specific impairments following restricted damage in certain regions of the frontal were found. First, left prefrontal lesions in the dorsomedial cortical region caused impairments on the phonological verbal fluency (mental flexibility) subtest of the FAB (Study 1) and on context retrieval in memory (Study 3). Second, the ventrolateral prefrontal cortex was demonstrated to be critical for disambiguation during context retrieval when multiple and unstable relationships between items and contexts in memory existed (Study 3).

In conclusion, the present results argue in favor of the frontal cortex being divided into many discrete regions responsible for specific aspects of cognitive processing, mainly the domain-general executive control of cognitive processes occurring in posterior regions of the brain. They also emphasize the importance of carefully selecting the patients with brain lesions in order to make claims about the functions of the specific areas.

References

Abela, A.R. & Chudasama, Y. (2013). Dissociable contributions of the ventral hippocampus and orbitofrontal cortex to decision-making with a delayed or uncertain outcome. *European Journal of Neuroscience, 37*: 640–647.

Ackermann, H., Daum, I. Schugens, M.M. & Grodd, W. (1996). Impaired procedural learning after damage to the left supplementary motor area (SMA). *Journal of Neurology, Neurosurgery and Psychiatry, 60*: 94-97.

Alexander, M.P. & Schmitt, M.A. (1980). The aphasia syndrome of stokre in the left anterior cerebral artery territory. *Archives of Neurology, 37*: 97-100.

Amiez, C. & Petrides, M. (2012). Neuroimaging evidence of the anatomo-functional organization of the human cingulate motor areas. *Cerebral Cortex*, Available: http://cercor.oxfordjournals.org/content/early/2012/11/06/cercor.bhs329.full. Accessed 12 March 2013.

Amiez, C., Sallet, J., Procyk, E. & Petrides, M. (2012). Modulation of feedback related activity in the rostral anterior cingulate cortex during trial and error exploration. *Neuroimage, 63*: 1078–1090.

Amunts, K., Weiss, P.H., Mohlberg, H., Pieperhoff, P., Eickhoff, S., Gurd, J.M., Marshall, J.C., Shah, N.J., Fink, G.R. & Zilles, K. (2004). Analysis of neural mechanisms underlying verbal fluency in cytoarchitectonically defined stereotaxic space -- the roles of Brodmann areas 44 and 45. *Neuroimage, 22*: 42-56.

Anderson, S.W., Damasio, H. & Tranel, D. (1990). Neuropsychological impairments associated with lesions caused by tumor or stroke. *Archives of Neurology, 47*: 397-405.

Archibald, S.J., Mateer, C.A. & Kerns, K.A. (2001). Utilization behavior: Clinical manifestation and neurological mechanisms. *Neuropsychological Review, 11*: 117-130.

Assal, G. (1985). Un aspect du comportement d'utilisation: la dependence vis-à-vis du langage écrit. *Revue Neurologique, 141*: 493-495.

Bachevalier, J. & Mishkin, M. (1986). Visual recognition impairment follows ventromedial but not dorsolateral prefrontal lesions in monkeys. *Behavioral Brain Research, 20*: 249-261.

Bachevalier, J. & Nemanic, S. (2008). Memory for spatial location and object-place associations are differently processed by the hippocampal formation, parahippocampal areas TH/TF and perirhinal cortex. *Hippocampus, 18*: 64-80.

Badre, D. & Wagner, A.D. (2007). Left ventrolateral prefrontal cortex and the cognitive control of memory. *Neuropsychologia, 45*: 2883-2901.

Balani, A.B., Soto, D. & Humphreys, G.W. (2009).Constraints on task-based control of behaviour following frontal lobe damage: A single-case study. *Cognitive Neuropsychology, 26*: 635-654.

Baldo, J.V., Shimamura, A.P., Delis, D.C., Kramer, J. & Kaplan, E. (2001). Verbal and design fluency in patients with frontal lobe lesions. *Journal of the International Neuropsychological Society, 7*: 586-596.

Bannur, U. & Rajshekhar, V. (2000). Post operative supplementary motor area syndrome: clinical features and outcome. *British Journal of Neurosurgery, 14*: 204-210.

Barbosa, I.G., Rocha, N.P., Huguet, R.B., Ferreira, R.A., Salgado, J.V., Carvalho, L.A., Pariante, C.M. & Teixeira, A.L. (2012). Executive dysfunction in euthymic bipolar disorder patients and its association with plasma biomarkers. *Journal of Affective Disorders, 137*: 151-155.

Beckmann, M., Johansen-Berg, H. & Rushworth, M.F. (2009). Connectivity based parcellation of human cingulate cortex and its relation to functional specialization. *Journal of Neuroscience, 29*: 1175–1190.

Benton, A. L. (1968). Differential behavioural effects in frontal lobe disease. *Neuropsychologia, 6*: 53-60.

Besnard, J., Allain, P., Osiurak, F., Aubin, G., Etcharry-Bouyx, F. & Le Gall, D. (2009). Contrôle exécutif et comportement d'utilisation d"objets: vers une dissociation. *La Revue de Neuropsychologie, 1*: 12-132.

Bigio, E.H., Vono, M., Satumtira, S., Adamson, J., Sontag, E., Hynan, L.S., White, C.L., Baker, M. & Hutton, M. (2001). Cortical synapse loss in progressive supranuclear palsy. *Journal of neuropathology and experimental neurology, 60*: 403-410.

Boccardi, E., Della Sala, S., Motto, C. & Spinnler, H. (2002). Utilisation behaviour consequent to bilateral SMA softening. *Cortex, 38*: 289-308.

Braak, H., Del Tredici, K., Rub, U., de Vos, R.A.I, Jansen Steur, E.N.H. & Braak, E. (2003). Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiology of Aging, 24*: 197-211.

Braak, H., Ghebremedhin, E., Rub, U., Bratzke, H & Del Tredici, K. (2004). Stages in the development of Parkinson's disease-related pathology. *Cell Tissue Research, 318*: 121-134.

Brazzelli, M., Colombo, N., Della Sala, S. & Spinnler, H. (1994). Spared and impaired cognitive abilities after bilateral frontal damage. *Cortex, 30*: 27-51.

Brazzelli, M. & Spinnler, H. (1998). An example of lack of frontal inhibition: the utilization behaviour. *European Journal of Neurology, 5*: 347–353.

Brodmann, K. (1908). Beitraege zur histologischen Lokalisation der Grosshirnrinde. VI. Mitteilung: Die Cortexgliederung des Menschen. *Journal für Psychologie und Neurologie (Lpz.), 10*: 231-246.

Brodmann, K. (1909). *Vergleichende Lokalisationslehre der Grosshirnrinde in ihren Prinzipien dargestellt auf Grund des Zellenbaues*. Leipzig: Barth.

Bugalho, P. & Vale, J. (2011). Brief cognitive assessment in the early stages of Parkinson disease. *Cognitive and Behavioral Neurology, 24*: 169-173.

Cadoret, G. & Petrides, M. (2007). Ventrolateral prefrontal neuronal activity related to active controlled memory retrieval in nonhuman primates. *Cerebral Cortex, 17*: i27-i40.

Cadoret, G., Pike, G.B. & Petrides, M. (2001). Selective activation of the ventrolateral prefrontal cortex in the human brain during active mnemonic processing. *European Journal Neuroscience, 14*: 1164-1170.

Carey, C.L., Kramer, J.H., Josephson, S.A., Mungas, D., Reed, B.R., Schuff, N., Weiner, M.W. & Chui, H.C. (2008). Subcortical lacunes are associated with executive dysfunction in cognitively normal elderly. *Stroke, 39*: 397-402.

Chapados, C. & Petrides, M. (2013). Impairment only on the verbal fluency subtest of the Frontal Assessment Battery after prefrontal lesions. *Brain, 136*: 2966-2978.

Chassagnon, S., Minotti, L., Kremer, S., Hoffmann, D. & Kahane, P. (2008). Somatosensory, motor, and reaching/grasping responses to direct electrical stimulation of the human cingulate motor areas. *Journal of Neurosurgery, 109*: 593–604.

Chow, T.W., Izenberg, A., Binns, M.A., Freedman, M., Stuss, D.T., Scott, C.J.M., Ramirez, J. & Black, S.E. (2008). Magnetic resonance imaging in frontotemporal dementia show subcortical atrophy. *Dementia and geriatric cognitive disorders, 26:* 79-88.

Cohen, O.S., Vakil, E., Tanne, D., Molshatzki, N., Nitsan, Z. & Hassin-Baer, S. (2012). The Frontal Assessment Battery as a tool for frontal lobe dysfunction in patients with Parkinson disease. *Journal of Geriatric Psychiatry and Neurology, 25*: 71-77.

Crosson, B., Sadek, J.R., Maron, L., Gökçay, D., Mohr, C.M., Auerbach, E.J., Freeman, A.J., Leonard, C.M. & Briggs, R.W. (2001). Relative shift in activity from medial to lateral frontal cortex during internally versus externally guided word generation. *Journal of Cognitive Neuroscience, 13*: 272-283.

Damian, M.F., Vigliocco, G. & Levelt, W.J.M. (2001). Effects of semantic context in the naming of pictures and words. *Cognition, 81*: B77-B86.

Degos, J.D., da Fonseca, N., Gray, F. & Cesaro, P. (1993). Severe frontal syndrome associated with infarcts of the left cingulate gyrus and the head of the right caudate nucleus. Brain, 116: 1541-1548.

De Renzi, E., Cavalleri, F. & Facchini, S. (1996). Imitation and utilization behaviour. *Journal of Neurology, Neurosurgery and Psychiatry, 61*: 396-400.

Dickson, D.W., Ahmed, Z., Algom, A.A., Tsuboi, Y. & Josephs, K.A. (2010). Neuropatholoogy of variants of progressive supranuclear palsy. *Current Opinion in Neurology, 23*: 394-400.

Dickson, D.W., Rademakers, R. & Hutton, M.L. (2007). Progressive supranuclear palsy: Pathology and genetics. *Brain Pathology, 17*: 74-82.

Dobbins, I.G., Foley, H., Schacter, D.L. & Wagner, A.D. (2002). Executive control during episodic retrieval: multiple prefrontal processes subserve source memory. *Neuron 35*: 98-99.

Duarte, A., Ranganath, C. & Knight, R.T. (2005). Effects of unilateral prefrontal lesions on familiarity, recollection, and source memory. *Journal of Neuroscience, 25*: 8333-8337.

Dubois, B., Slachevsky, A., Litvan, I. & Pillon, B. (2000). The FAB A frontal assessment battery at bedside. *Neurology, 55*: 1621-1626.

Duffau, H. (2012). The "frontal syndrome" revisited: Lessons from electrostimulation mapping studies. *Cortex, 48*: 120-131.

Dum, R.P. & Strick, P.L (1993). Cingulate motor areas. In B. Vogt & M. Gabriel (Eds.), *Neurobiology of cingulate cortex and limbic thalamus: a comprehensive handbook* (pp. 415–441). Boston: Birkhäuser.

Dum, R.P. & Strick, P.L. (2002). Motor areas in the frontal lobe of the primate. *Physiology & Behavior, 77*: 677–682.

Duncan, J. & Miller, E.K. (2002). Cognitive focus through adaptive neural coding in the primate prefrontal cortex. In D.T. Stuss & R.T. Knight (Eds.), *Principles of frontal lobe function* (pp. 278-291). New York: Oxford University Press.

Economo, C. & Koskinas, G.N. (1925). *Die Cytoarchitektonik der Hirnrinde Des Erwachsenen Menschen.* Vienna: Springer.

Eichenbaum, H., Yonelinas, A.P. & Ranganath, C. (2007). The medial temporal lobe and recognition memory. *Annual Review of Neuroscience, 30*: 123-152.

Eslinger, P.J., Warner, G.C., Grattan, L.M. & Easton, J.D. (1991). "Frontal lobe" utilization behavior associated with paramedian thalamic infarction. *Neurology, 41*: 450-452.

Fellows, L.K. & Farah, M.J. (2005). Is anterior cingulate cortex necessary for cognitive control? *Brain, 128*: 788-796.

Freedman, M. Alexander, M.P. & Naeser, M.A. (1984). Anatomic basis of transcotical motor aphasia. *Neurology, 34*: 409-417.

Fujii, T., Suzuki, M., Okuda, J., Ohtake, H., Tanji, K., Yamaguchi, K., Itoh, M. & Yamadori, A. (2004). Neural correlates of context memory with real-world events. *Neuroimage, 21*: 1596-1603.

Fukui, T., Hasegawa, Y., Sugita, K. & Tsukagoshi, H. (1993). Utilizaion behavior and concomitant motor neglect by bilateral frontal lobe damage. *European Neurology, 33*: 325-330.

Ghaki, J., Tennis, M., Growdon, J., Hoffman, E. & Johnson, K. (1995). Environment-driven responses in progressive supranuclear palsy. *Journal of the Neurological Sciences, 130*: 104-111.

Gilman, S., Wenning, G.K., Low, P.A., Brooks, D.J., Mathias, C.J., Trojanowski, J.Q., Wood, N.W., Colosimo, C., Dürr, A., Fowler, C.J., Kaufman, H., Klockgether, T., Lees, A., Poewe, W., Quinn, N., Revesz, T., Robertson, D., Sandroni, P. Seppi, K. & Vidailhet, M. (2008). Second consensus statement on the diagnosis of multiple system atrophy. *Neurology, 71*: 670-676.

Goldberg, G. (1985). Supplementary motor area structure and function: Review and hypotheses. *Behavioral and Brain Sciences, 8*: 567-588.

Goldberg, G., Mayer, N.H. & Toglia, J.U. (1981). Medial frontal cortex infarction and the alien hand sign. *Archives of Neurology, 38*: 683-686.

Gorno-Tempini, M.-L., Dronkers, N.F., Rankin, K.P., Ogar, J.M., Phengrasamy, L., Rose, H.J., Johnson, J.K., Weiner, M.W. & Miller, B.L. (2004). Cognition and anatomy in three variants of primary progressive aphasia. *Annals of Neurology, 55*: 335-346.

Hashimoto, R., Yoshida, M. & Tanaka, Y. (1995). Utilization behavior after right thalamic infarction. *European Neurology, 35*: 58-62.

Hebb, D.O. (1939). Intelligence in man after large removal of cerebral tissue: report of four left frontal lobe cases. *The Journal of General Psychology, 21:* 73-87.

Hebb, D.O. (1945). Man's frontal lobes: a critical review. *Archives of Neurology and Psychiatry, 54*: 10-24.

Heflin, L.H., Laluz, V., Jang, J., Ketelle, R., Miller, B.L. & Kramer, J.H. (2011). Let's inhibit our excitement: The relationship between Stroop, behavioral disinhibition, and the frontal lobes. *Neuropsychology, 25*: 655-665.

Henry, J.D. & Crawford, J.R. (2004). A meta-analytic review of verbal fluency performance following focal cortical lesions. *Neuropsychology, 18*: 284-295.

Iavarone, A., Lorè, E., De Falco, C., Milan, G., Mosca, R., Pappatà, S., Galeone, F., Sorrentino, P., Scognamiglio, M. & Postiglione, A. (2011). Dysexecutive performance of healthy oldest old subjects on the Frontal Assessment Battery. *Aging Clinical and Experimental Research, 23*: 351-356.

Incisa della Rocchetta, A. & Milner, B. (1993). Strategic search and retrieval inhibition: the role of the frontal lobes. *Neuropsychologia, 31*: 503-524.

Ishihara, K., Nishino, H., Maki, T., Kawamura, M. & Murayama, S. (2002). Utilization behavior as a white matter disconnection syndrome. *Cortex, 38*: 379-387.

Janowsky, J.S., Shimamura, A.P. & Squire, L.R. (1989). Source memory impairment in patients with frontal lobe lesions. *Neuropsychologia, 27*: 1043-1056.

Jefferies, E. & Lambon Ralph, M.A. (2006). Semantic impairment in stroke aphasia versus semantic dementia: a case-series comparison. *Brain, 129*: 2132-2147.

Jellinger, K.A. (2011). Neuropathology of sporadic Parkinson's disease: evaluation and changes of concepts. *Movement Disorder, 27*: 8-30.

Johansen-Berg, H., Behrens, T.E.J., Robson, M.D., Drobnjak, I., Rushworth, M.F.S., Brady, J.M., Smith, S.M., Higham, D.J. & Matthews, P.M. (2004). Changes in connectivity profiles define functionally distinct regions in human medial frontal cortex. *Proceedings of the National Academy of Science USA, 101*: 13335–13340.

Johnson, M. K., Hashtroudi, S. & Lindsay, D.S. (1993). Source monitoring. *Psychological Bulletin, 114:* 3-28.

Jones-Gotman M. & Milner B. (1977). Design Fluency: The invention of nonsense drawings after focal cortical lesions. *Neuropsychologia*, *15*: 653-674.

Jürgens, U. (1984). The efferent and afferent connections of the supplementary motor area. *Brain Research, 300*: 63-81.

Jürgens, U. (2009). The neural control of vocalization in mammals: a review. *Journal of Voice, 23*: 1–10.

Kanno, S., Saito, M., Hayashi, A., Uchiyama, M., Hiraoka, K., Nishio, Y., Hisanaga, K. & Mori E. (2012). Counting-backward test for executive function in idiopathic normal pressure hydrocephalus. *Acta Neurologica Scandinavia, 126*: 279–286.

Kaszas, N., Balas, I., Kallai, J., Aschermann, Z., Kerekes, Z., Komoly, S., Nagy, F., Janszky, J., Lucza, T. & Karadi, K. (2012). Sensitivity and specificity of Addenbrooke's Cognitive Examination, Mattis Dementia Rating Scale, Frontal Assessment Battery and Mini Mental State Examination for diagnosing dementia in Parkinson's disease. *Parkinsonism and Related Disorders, 18*: 553-556.

Kostopoulos, P., Albanese, M.-C. & Petrides, M. (2007). Ventrolateral prefrontal cortex and tactile memory disambiguation in the human brain. *Proceedings of the National Academy of Science USA, 104*: 10223-10228.

Kostopoulos, P. & Petrides, M. (2003). The mid-ventrolateral prefrontal cortex: insights into its role in memory retrieval. *European Journal of Neuroscience, 17*: 1489-1497.

Kostopoulos, P. & Petrides, M. (2008). Left mid-ventrolateral prefrontal cortex: underlying principles of function. *European Journal of Neuroscience, 27*: 1037-1049.

Krainik, A. Lehéricy, S., Duffau, H., Vlaicu, M., Poupon, F., Capelle, L., Cornu, P., Clemenceau, S., Sahel, S., Valery, C.-A., Boch, A.-L., Mangin, J.-F., Le Bihan, D. & Marsault, C. (2001). Role of the supplementary motor area in motor defcit following medial frontal lobe surgery. *Neurology, 57*: 871-878.

Krainik, A. Lehéricy, S., Duffau, H., Capelle, L., Chainay, H., Cornu, P., Cohen, L., Boch, A.-L., Mangin, J.-F., Le Bihan, D. & Marsault, C. (2003). Post-operative speech disorder after medial frontal surgery: role of the supplementary motor area. *Neurology, 60*: 587-594.

Kucera, H. & Francis, W.N. (1967). *Computational Analysis of Present-Day American English.* Providence: Brown University Press.

Kugo, A., Terada, S., Ata, T., Ido, Y., Kado, Y., Ishihara, T., Hikiji, M., Fujisawa, Y., Sasaki, K. & Kuroda, S. (2007). Japanese version of the Frontal Assessment Battery for dementia. *Psychiatry Research, 153*: 69–75.

Laplane, D., Degos, J.D., Baulac, M. & Gray, F. (1981). Bilateral infacrtion of the anterior cingulated gyri and of the fornices. *Journal of the Neurological Sciences, 51*: 289-300.

Lee, S.E., Rabinovich, G.D., Mayo, M.C., Wilson, S.M., Seeley, W.W., DeArmond, S.J., Huang, E.J., Trojanowski, J.Q., Growdon, M.E., Jang, J.Y., Sidhu, M., See, T.M., Karydas, A.M., Gorno-Tempini, M.-L., Boxer, A.L., Weiner, M.W., Geschwind, M.D., Rankin, K.P. & Miller, B.L. (2011). Clinicopathological correaltions in corticobasal degeneration. *Annals of Neurology, 70*: 327-340.

Lezak, M. D. (1995). *Neuropsychological Assessment* (3rd Ed.). New York: Oxford University Press.

Lhermitte, F. (1983). 'Utilization Behaviour' and its relation to lesions of the frontal lobes. *Brain, 106*: 237-255.

Lhermitte, F., Pillon, B. & Serdaru, M. (1986). Human autonomy and the frontal lobes. Part I: Imitation and utilization behavior: A neuropsychological study of 75 patients. *Annals of Neurology, 19*: 326-334.

Ling, H., O'Sullivan, S.S., Holton, J.L., Revesz, T., Massey, L.A., Williams, D.R., Paviour, D.C. & Lees, A.J. (2010). Does corticobasal degeneration exist? A clinicopathological re-evaluation. *Brain, 133*: 2045-2057.

Lipton, A.M., Ohman, K.A., Womack, K.B., Hynan, L.S., Ninman, E.T. & Lacritz, L.H. (2005). Subscores of the FAB differentiate frontotemporal lobar degeneration from AD. Neurology, 65: 726-731.

Lupker, S.J. & Katz, A.N. (1981). Input, decision, and response factors in picture-word interference. *Journal of Experimental Psychology: Human Learning and Memory, 7*: 269-282.

Luria, A. R. (1969). Frontal lobe syndromes. In P. J. Vinken and G. W. Bruyx (Eds.) *Handbook of Clinical Neurology* (Vol. 2, pp. 725-757), Amsterdam: North-Holland.

Madseu, J.C., Schoene, W.C. & Funkenstein, H. (1978). Aphasia following infarction of the left supplementary motor area. *Neurology, 28*: 1220-1223.

Malkova, L. & Mishkin, M. (2003). One-trial memory for object-place associations after separate lesions of hippocampus and posterior parahippocampal region in the monkey. *Journal of Neuroscience, 23*: 1956-1965.

Margulies, D.S. & Petrides, M. (2013). Distinct parietal and temporal connectivity profiles of ventrolateral frontal areas involved in language production. *Journal of Neuroscience, 33:* 16846-16852.

Milner, B. (1963). Effect of different brain lesions on card Sorting. *Archives of Neurology, 9*: 90-100.

Milner, B. (1964). Some effects of frontal lobectomy in man. In J.M. Warren & K. Akeri (Eds.), *The frontal granular cortex and behaviour* (pp. 313-331). New York: McGraw-Hill.

Milner, B. (1971). Interhemispheric differences in the localization of psychological processes in man. *British Medical Bulletin, 26*: 272-277.

Milner, B. (1982). Some cognitive effects of frontal-lobe lesions in man. *Philosophical Transactions of the Royal Society of London B, 298*: 211-226.

Mishkin, M. (1982). A memory system in the monkey. *Philosophical Transactions of the Royal Society of London B: Biological Sciences, 298*: 85-95.

Mitchell, K.J. & Johnson, M.K. (2009). Source monitoring 15 years later: what have we learned from fMRI about the neural mechanisms of source memory? *Psychological Bulletin, 135*: 638-677.

Miyashita, Y. (2004). Cognitive Memory: Cellular and Network Machineries and Their Top-down Control. Science, 306: 435-440.

Miyoshi, N., Kazui, H., Ogino, A., Ishikawa, M., Miyake, H., Tokunaga, H., Ikejiri, Y. & Takeda, M. (2005). Association between cognitive impairment and gait disturbance in patients with idiopathic normal pressure hydrocephalus. *Dementia and Geriatric Cognitive Disorders, 20*: 71-76.

Mok, V.C.T., Wong, A., Yim, P., Fu, M., Lam, W.W.M., Hui, A.C., Yau, C. & Wong, K.S. (2004). The validity and reliability of the Chinese frontal Assessment Battery in evaluating executive dysfunction among Chinese patients with small subcortical infarct. *Alzheimer Disease & Associated Disorders, 18*: 68-74.

Moorhouse, P., Gorman, M. & Rockwood, K. (2009). Comparison of EXIT-25 and the Frontal Assessment Battery for evaluation of executive

dysfunction in patients attending a memory clinic. *Dementia and geriatric cognitive disorders, 27:* 424-428.

Morris, R., Pandya, D.N. & Petrides, M. (1999). Fiber system linking the middorsolateral frontal cortex with the retrosplenial/presubicular region in the rhesus monkey. *Journal of Comparative Neurology, 407*: 183-192.

Morris, R.G.M., Garrud, P., Rawlins, J.N.P. & O'Keefe, J. (1982). Place navigation impaired in rats with hippocampal lesions. *Nature 297*: 681-683.

Moscovitch, M. (1992). Memory and working-with-memory: A component process model based on modules and central systems. *Journal of Cognitive Neuroscience, 4*: 257-267.

Nachev, P., Kennard, C. & Husain, M. (2008). Functional role of the supplementary and pre-supplmentary motor areas. *Nature Reviews Neurosciences, 9*: 856-869é

Nyhus, E. & Barcelo, F. (2009). The Wisconsin Card Sorting Test and the cognitive assessment of prefrontal executive functions: a critical update. *Brain and Cognition, 71*: 437-451.

Pai, M.-C. (1999). Supplementary motor area aphasia: a case report. *Clinical Neurology and Neurosurgery, 101*: 29-32.

Pan, P.L., Song, W., Yang, J., Huang, R., Chen, K., Gong, Q.Y., Zhong, J.G., Shi, H.C. & Shang, H.F. (2012). Gray matter atrophy in behavioural variant of frontotemporal dementia: a meta-analysis of voxel-based morphometry studies. *Dementia and geriatric cognitive disorders*, 33: 141-148.

Papp, M.I. & Lantos, P.L. (1994). The distribution of oligodendroglial inclusions in multiple system atrophy and its relevance to clinical symptomatology. *Brain, 117*: 235-243.

Park, H., Shannon, V., Biggan, J. & Spann, C. (2012). Neural activity supporting the formation of associative versus source memory. *Brain Research, 1471*: 81-92.

Parkinson, J.K., Murray, E.A. & Mishkin, M. (1988). A selective mnemonic role for the hippocampus in monkeys: Memory for the Location of Objects. *Journal of Neuroscience, 8*: 4159-4167.

Passingham, R.E. (1993). *The Frontal Lobes and Voluntary Action*. Oxford: Oxford University Press.

Paus, T., Petrides, M., Evans, A.C. & Meyer, E. (1993). Role of the human anterior cingulated cortex in the control of oculomotor, manual and speech responses: a positron emission tomography study. *Journal of Neurophysiology, 70*: 453-469.

Pavio, A., Yuille, J.C. & Madigan, S.A. (1968). Concreteness, imagery and meaningfulness values for 925 words. *Journal of Experimental Psychology, 76* (Monograph Supplement): 125.

Penfield, W. & Welch, K. (1951). The supplementary motor area of the cerebral cortex: a clinical and experimental study. *Archives of Neurology and Psychiatry, 66*: 289-317.

Perret, E. (1974). The left frontal lobe of man and suppression of habitual responses in verbal categorical behaviour. *Neuropsychologia, 12*: 323-330.

Petrides, M. (1985). Deficits on conditional associative-learning tasks frontal- and temporal-lobe lesions in man. *Neuropsychologia, 23*: 601-614.

Petrides, M. (1991). Monitoring of selections of visual stimuli and the primate frontal cortex. *Proceedings of the Royal Society of London B, 246*: 293-298.

Petrides, M. (1994). Frontal lobes and working memory: evidence from investigations of the effects of cortical excisions in nonhuman primates. In F. Boller & J. Grafman (Eds.), *Handbook of Neuropsychology* (Vol. 9, pp. 59-82), New York: Elsevier.

Petrides, M. (1995). Impairments on nonspatial self-ordered and externally ordered working memory tasks after lesions of the mid-dorsal part of the lateral frontal cortex in the monkey. *Journal of Neuroscience, 15*: 359-375.

Petrides, M. (1996). Specialized systems for the processing of mnemonic information within the primate frontal cortex. *Philosophical Transactions of the Royal Society, London B, 351*: 1455-1462.

Petrides, M. (2000a). Frontal lobes and memory. In F. Boller & J. Grafman (Eds.), *Handbook of Neuropsychology* (2nd ed., Vol. 2, pp. 67-84). Amsterdam: Elsevier.

Petrides, M. (2000b). Dissociable roles of mid-dorsolateral prefrontal and anterior inferotemporal cortex in visual working memory. *Journal of Neuroscience, 20*: 7496-7503.

Petrides, M. (2002). The mid-ventrolateral prefrontal cortex and active memory retrieval. *Neurobiology of Learning and Memory, 78*: 528-538.

Petrides, M. (2005). Lateral prefrontal cortex: architectonic and functional organization. *Philosophical Transactions of the Royal Society of London B Biological Sciences, 360*: 781-795.

Petrides, M., Alivisatos, B. & Evans, A.C. (1995). Functional activation of the human ventrolateral frontal cortex during mnemonic retrieval of verbal information. *Proceedings of the National Academy of Science, 92*: 5803-5807.

Petrides, M. & Milner, B. (1982). Deficits on subject-ordered tasks after frontal- and temporal-lobe lesions in man. *Neuropsychologia, 20*: 249-262.

Petrides, M. & Pandya, D.N. (1994). Comparative architectonic analysis of the human and the macaque frontal cortex. In F. Boller & J. Grafman (Eds.), *Handbook of neuropsychology*. (Vol. 9, pp. 17–58). Amsterdam: Elsevier.

Petrides, M. & Pandya, D.N. (1999). Dorsolateral prefrontal cortex: Comparative cytoarchitectonic analysis in the human and the macaque brain and corticocortical connection patterns. *European Journal of Neuroscience, 11*: 1011-1036.

Petrides, M. & Pandya, D.N. (2002). Comparative cytoarchitectonic analysis in the human and the macaque ventrolateral prefrontal cortex and corticocortical connection patterns in the monkey. *European Journal of Neuroscience, 16*: 291-310.

Phelps, E., Hyder, F., Blamire, A.M. & Shulman, R.G. (1997). FMRI of the prefrontal cortex during overt verbal fluency. *NeuroReport, 8*: 561-565.

Picard, N. & Strick, P.L. (1996). Motor areas of the medial wall: a review of their location and functional activation. *Cerebral Cortex, 6*: 342–353.

Picard, N. & Strick, P.L. (2001). Imaging the premotor areas. *Current Opinion in Neurobiology, 11*: 663–672.

Plaza, M., du Boullay, V., Perrault, A., Chaby, L. & Capelle, L. (2013). A case of bilateral frontal tumours without "frontal syndrome". *Neurocase: The Neural Basis of Cognition*, doi: 10.1080/13554794.2013.826696.

Possin, K.L., Chester, S.K., Laluz, V., Bostrom, A., Rosen, H.J., Miller, B.L. & Kramer, J.H. (2009). The frontal-anatomic specificity of design fluency repetitions and their diagnostic relevance for behavioral variant frontotemporal dementia. *Journal of the International Neuropsychology Society, 18*: 834-844.

Racy, A., Jannotta, F.S. & Lehner, L.H. (1979). Aphasia resulting from occlusion of the left anterior cerebral artery. *Archives of Neurology, 36*: 221-224.

Reitan, R.M. & Wolfson, D. (1995). Category Test and Trail Making Test as measures of frontal lobe functions. *The Clinical Neuropsychologist, 9*: 50-56.

Robinson, G., Blair, J. & Cipolotti, L. (1998). Dynamic aphasia: an inability to select between competing verbal responses? *Brain, 121*: 77-89.

Robinson, G., Shallice, T., Bozzali, M. & Cipolotti, L. (2012). The differing roles of the frontal cortex in fluency tasks. *Brain, 135*: 2202-2214.

Roca, M., Manes, F., Gleichgerrcht, E., Watson, P., Ibanez, A., Thompson, R., Torralva, T. & Duncan, J. (2013). Intelligence and executive functions in frontotemporal dementia. *Neuropsychologia, 51*: 725-730.

Roca, M., Parr, A., Thompson, R., Woolgar, A., Torralva, T., Antoun, N., Manes, F. & Duncan, J. (2010). Executive function and fluid intelligence after frontal lobe lesions. *Brain, 133*: 234-247.

Rorden, C. & Brett, M. (2000). Stereotaxic dysplay of brain lesions. *Behavioral Neurology, 12*: 191-200.

Rorden, C., Karnath, H.O. & Bonilha, L. (2007). Improving lesion-symptom mapping. *Journal of Cognitive Neuroscience, 19*: 1081-1088.

Rosen, H.J., Gorno-Tempini, M.-L., Goldman, W.P., Perry, R.J., Schuff, N., Weiner, M., Feiwell, R., Kramer J.H. & Miller, B.L. (2002). Patterns of brain atrophy in frontotemporal dementia and semantic dementia. *Neurology, 58*: 198-208.

Ross, E.D. (1980). Left medial parietal lobe and receptive language functions: mized transcortical aphasia after left anterior cerebral artery infarction. *Neurology, 30*: 144-151.

Rostomily, R.C., Berger, M.S., Ojemann, G.A. & Lettich, E. (1991). Postoperative deficits and functional recovery following removal of tumors involving the dominant hemisphere supplementary motor area. *Journal of Neurosurgery, 75*: 62-68.

Royall, D.R., Mahurin, R.K. & Gray, K. (1992). Bedside assessment of executive dyscontrol: The executive interview. *Journal of American Geriatrics Society, 40*: 1221-1226.

Rubens, A.B. (1975). Aphasia with infarction in the territory of the anterior cerebral artery. *Cortex, 11*: 239-250.

Rudd, R. Maruff, P., MacCupsie-Moore, C., Velakoulis, D., Brewer, W. & Pantelis, C. (1998). Stimulus relevance in eliciting utilization behaviour: Case study in a patient with caudate lesion. *Cognitive Neuropsychiatry, 3*: 287-298.

Sarkissov, S.A., Filimonoff, I.N., Kononowa, E.P., Preobraschenskaja, I.S. & Kukuew, L.A. (1955). *Atlas of the Cytoarchitectonics of the Human Cerebral Cortex.* Moskow: Medgiz.

Schacter, D.L. (1995). *Memory distortion: how minds, brains and societies reconstruct the past.* Cambrdge, MA: Harvard University Press.

Scoville, W.B. & Milner, B. (1957). Loss of recent memory after bilateral hippocampal lesions. *Journal of Neurology, Neurosurgery and Psychiatry, 20*: 11-21.

Seltman, R.E. & Matthews, B.R. (2012). Frontotemporal lobar degeneration: epidemiology, pathology, diagnosis and management. *CNS Drugs, 10*: 842-870.

Shallice, T., Burgess, P.W., Schon, F. & Baxter, D.M. (1989). The origins of utilization behaviour. *Brain, 112*: 1587-1598.

Shallice, T., Stuss, D.T., Alexander, M.P., Picton, T.W. & Derkzen, D. (2008). The multiple dimensions of sustained attention. *Cortex, 44*: 794-805.

Shimamura, A.P., Janowsky, J.S. & Squire, L.R. (1990). Memory for the temporal order of events in patients with frontal lobe lesions and amnesic patients. *Neuropsychologia, 28*: 803-813.

Shimamura, A.P. & Squire, L.R. (1987). A neuropsychological study of fact memory and source amnesia. *Journal of Experimental Psychology: Learning, Memory and Cognition, 13*: 464-473.

Smith, M.L., Leonard, G., Crane, J. & Milner, B. (1995). The effects of frontal- or temporal-lobe lesions on susceptibility to interference in spatial memory. *Neuropsychologia, 33*: 275-285.

Smith, M.L. & Milner, B. (1981). The role of the right hippocampus in the recall of spatial location. *Neuropsychologia, 19*: 781–793.

Smith, M.L. & Milner, B. (1984). Differential effects of frontal-lobe lesions on cognitive estimation and spatial memory. *Neuropsychologia, 22*: 697–705.

Smith, M.L. & Milner, B. (1989). Right hippocampal impairment in the recall of spatial location: encoding deficit or rapid forgetting? *Neuropsychologia, 27*: 71–81.

Squire, L.R. & Zola-Morgan, S. (1991). The medial temporal lobe memory system. *Science, 253*: 1380-1386.

Steele, J.C., Richardson, J.C. & Olszewski, J. (1964). Progressive Supranuclear Palsy. *Archives of Neurology, 10*: 333-359.

Stuss, D.T. (2007). New approaches to prefrontal lobe testing. In B.L. Miller & J.L. Cummings (Eds.), *The human frontal lobes: functions and disorders* (2nd ed., pp. 292-305). New York: The Guilford Press.

Stuss, D.T. (2011). Functions of the frontal lobes: relation to executive functions. *Journal of the International Neuropsychology Society, 17*: 759-765.

Stuss, D.T. & Alexander, M.P. (2005). Does damage to the frontal lobes produce impairment in memory? *Current Directions in Psychological Science, 14*: 84-88.

Stuss, D.T. & Alexander, M.P. (2007). Is there a dysexecutive syndrome? *Philosophical Transactions of the Royal Society of London B: Biological Sciences, 362*: 901-915.

Stuss, D.T., Alexander, M.P., Hamer, L., Palumbo, C., Dempster, R., Binns, M., Levine, B. & Izukawa, D. (1998). The effects of focal anterior and posterior brain lesion on verbal fluency. *Journal of the International Neuropsychological Society, 4*: 265-278.

Stuss, D.T., Alexander, M.P., Shallice, T., Picton, T.W., Binns, M.A., Macdonald, R., Borowiec, A. & Katz, D.I. (2005). Multiple frontal systems controlling response speed. *Neuropsychologia, 43*: 396-417.

Stuss, D.T., Benson, D.F., Clermont, R., Della Malva, C.L., Kaplan, E.F. & Weir, W.S. (1986). Language functioning after bilateral prefrontal leukotomy. *Brain and Language, 28*: 66-70.

Stuss, D.T. & Knight, R.T. (2013). *Principles of frontal lobe function* (2nd Ed.). Oxford: Oxford University Press.

Taphoorn, M.J.B. & Klein, M. (2004). Cognitive deficits in adult patients with brain tumours. *Lancet Neurology, 3*: 159-168.

Terada, T., Obi, T., Miyajima, H. & Mizoguchi, K. (2010). Assessing frontal lobe function in patients with amyotrophic lateral sclerosis by frontal assessment battery. *Rinsho shinkeigaku = Clinical Neurology, 50*: 379-384.

Teuber, H.L. (1955). Physiological psychology. *Annual Review of Psychology, 9*:267-296.

Thaiss, L. & Petrides, M. (2003). Source versus content memory in patients with a unilateral frontal cortex or a temporal lobe excision. *Brain, 126*: 1112-1126.

Thaiss, L. & Petrides, M. (2008). Autobiographical memory of the recent past following frontal cortex or temporal lobe excisions. *European Journal of Neuroscience, 28*: 829-840.

Thompson-Schill, S.L., D'Esposito, M., Aguirre, J.K. & Farah, M.J. (1997). Role of the left inferior prefrontal cortex in retrieval of semantic knowledge: A reevaluation. *Proceedings of the National Academy of Science, 94*: 14792-14797.

Tsuchida, A., Doll, B.B. & Fellows, L. (2010). Beyond reversal: A critical role for human orbitofrontal cortex in flexible learning from probabilistic feedback. *Journal of Neuroscience, 30*: 16868-16875.

Tulving, E. (1972). Episodic and semantic memory. In E. Tulving & W. Donaldson (Eds.), *Organization and Memory* (pp.382-403). New York: Academic Press.

Tulving, E. (1983). *Elements of episodic memory*. Oxford: Clarendon Press.

Valverde, A.H., Limenez-Escrig, A., Gobernado, J. & Baron, M. (2009). A short neuropsychologic and cognitive evaluation of frontotemporal dementia . *Clinical Neurology and Neurosurgery, 111*: 251–255.

Wakabayashi, K. & Takahashi, H. (2006). Cellular pathology in multiple system atrophy. *Neuropathology, 26*: 338-345.

Wenning, G.K., Stefaniva, N., Jellinger, K.A., Poewe, W. & Schlossmacher, M.G. (2008). Multiple system atrophy: A primary oligodendrogliopathy. *Annals of Neurology, 64*: 239-246.

Withwell, J.L., Master, A.V., Avula, R., Kantarci, K., Eggers, S.D., Edmonson, H.A., Jack, C.R. & Josephs, K.A., (2011). Clinical correlates of white matter tract degeneration in progressive supranuclear palsy. *Archives of Neurology, 68*: 753-760.

Whitwell, J.L., Przybelski, S.A., Weigand, S.D., Ivnik, R.J., Vemuri, P., Gunter, J.L., Senjem, M.L., Shiung, M.M., Boeve, B.F., Knopman, D.S., Parisi, J.E., Dickson, D.W., Petersen, R.C., Jack, C.R. & Josephs, K.A. (2009). Distinct anatomical subtypes of the behavioural variant of frontotemporal dementia: a cluster analysis study. *Brain, 132*: 2932-2946.

Yoshida, H., Terada, S., Sato, S., Kishimoto, Y., Ata, T., Ohshima, E., Honda, H., Ishihara, T. & Kuroda, S. (2009). Frontal Assessment Battery and Brain Perfusion Imaging in Early Dementia. *Dementia and Geriatric Cognitive Disorders, 27*: 133–138.

Zago-Gomes, M.d.P. & Nakamura-Palacios, E.M. (2009). Cognitive components of frontal lobe functions in alcoholics classified according to Lesch's typology. *Alcohol & Alcoholism*, 44: 449-457.

Zentner, J., Hufnagel, A., Pechstein, U., Wolf, H.K. & Schramm, J. (1996). Functional results after resective procedures involving the supplementary motor area. *Journal of Neurosurgery, 85*: 542-549.

Ziegler, W., Kilian, B. & Deger, K. (1997). The role of the left mesial frontal cortex in fluent speech: evidence from a case of left supplementary motor area hemorrhage. *Neuropsychologia, 35*: 1197-1208.

Appendix

Description of the patients

The selection of patients with lesions strictly restricted to the cortical region of interest was crucial in order to make specific and causal anatomo-functional claims. Because we were interested in examining functions of the frontal cortex, only patients with circumscribed lesions to the frontal cortex and no more than the immediately subjacent white matter were included. . In addition, in order to control for the general effect of having a brain injury, patients with lesions in another part of the brain were also included in the studies as controls. These were patients with lesions restricted to the temporal lobe with damage resulting from the same aetiologies. Consequently, any observed functional impairment in patients with frontal cortical damage could be ascribed solely to the frontal cortex. Most patients had undergone brain surgery at the Montreal Neurological Institute for the relief of focal epileptic seizures or removal of cerebral tumour. In addition, four patients had suffered a cerebrovascular accident. None of the patients had co-morbid neurological or psychiatric disorders or were having chemotherapy or radiotherapy at the time of testing. No participants with a full-scale WASI score below 79 were included. These excluding criteria were chosen in order to limit the effect of other potential confounding factors on cognitive functions. The patients participated in at least one of the three studies described in this thesis.

Patients with frontal cortical lesions

Twenty-six patients with lesions restricted to the frontal cortex were included. Fourteen patients had lesions in the left frontal cortex, 11 had lesions in the right frontal cortex and one patient had the supplementary motor area (SMA) removed bilaterally. All removals spared the primary motor cortical region on the precentral gyrus, except for two patients (F005 and F017). Nineteen of the patients had undergone neurosurgery for the resection of a low-grade tumour and four for the relief of idiopathic epilepsy; three patients had suffered a cerebrovascular accident. The characteristics of each patient with left, right and bilateral prefrontal cortex lesions are presented in Table 1a, 1b and 1c, respectively.

The post-operative magnetic resonance images (MRI) were available for nine patients with frontal cortex lesions. For 13 patients, tracings of the lesions by an experienced neurologist, displayed on the standard Montreal Neurological Institute (MNI) brain with MRIcro software (Rorden & Brett, 2000), were obtained. The extent and precise location of the frontal lesions were assessed from those two sources. Unfortunately, the anatomical data were missing for four patients in the frontal group.

Table 1. Characteristics of patients with prefrontal cortex lesions
(a) Left-sided lesions

Patient	Studies[1]	Age for 1, 3	Age for 2	Gender	Handedness	FirstLanguage /Tested	Education (years)	Time[2] for 1, 3	Time for 2	Aetiology
F001	1, 2, 3	52	54	Female	Right	French	16	OR1: 15:3 OR2: 13:5	OR1: 17:8 OR2: 15:10	Meningioma Grade I
F005	1, 3	46	-	Male	Right	English	14	5:6	-	Oligodendroglioma Grade II
F006	1, 2, 3	51	54	Male	Right	French	11	1:5	4:3	Oligodendroglioma Grade II
F007	1, 2, 3	51	53	Male	Right	French	16	0:11	2:10	Infiltrating astrocytoma Grade II
F008	1, 3	39	-	Male	Right	English	20	1:1	-	Oligodendroglioma Grade II
F010	1, 3	27	-	Female	Right	English	16	OR1: 6:2 OR2: 1:1	-	Oligodendroglioma Grade II
F012	1, 3	39	-	Female	Right	French	14	1:8	-	Astrocytoma Grade II
F017	1, 2	69	69	Female	Right	Tagalog/ English	12	4:8	4:8	Cerebrovascular accident
F018	1, 2	65	65	Female	Left	English	16	2:5	2:5	Meningioma Grade I
F021	1, 2, 3	50	50	Male	Right	German/ English	21	5:1	5:1	Anaplastic oligodendroglioma Grade III
F023	1, 2, 3	55	55	Female	Right	Polish/ English	12	1:9	1:9	Meningioma grade II
F024	1, 2, 3	42	42	Female	Right	French	18	5:4	5:4	Cerebrovascular accident
F025	1, 2	56	56	Male	Right	English	18	OR1: 6:9 OR2: 6:7	OR1: 6:9 OR2: 6:7	Glioblastoma Grade III-IV
F026	1, 2, 3	37	37	Female	Right	French	11	OR1: 15:1 OR2: 2:9	OR1: 15:1 OR2: 2:9	Epileptogenic osteoma and scar tissues

[1] 1: Frontal Assessment Battery; 2: Utilization Behaviour; 3: Context Retrieval Memory Task
[2] Time corresponds to time elapsed between the surgery/stroke and the testing in years:months

(b) Right-sided lesions

Patient	Studies [1]	Age for 1, 3	Age for 2	Gender	Handedness	First Language/ Tested	Education (years)	Time for 1, 3	Time for 2	Aetiology
F004	1, 2, 3	61	63	Female	Right	French	20	5:10	8:4	Meningioma Grade I
F009	1, 2, 3	57	59	Male	Right	French	10	0:11	2:8	Astrocytoma Grade II
F011	1, 3	55	-	Female	Right	French	15	0:5	-	Oligoastrocytoma grade I-II
F014	1, 2, 3	52	52	Female	Right	Portuguese/ English	17	1:11	1:11	Tumour Grade I
F015	1, 2, 3	43	43	Female	Left	French	15	16:5	16:5	Idiopathic epilepsy
F016	1, 2, 3	40	40	Female	Right	Romanian/ French		OR1: 1:10 OR2: 1:7	OR1: 1:10 OR2: 1:7	Meningioma Grade II
F019	1, 2, 3	58	58	Female	Right	English	12	2:6	2:6	CVA
F020	1, 2, 3	49	49	Female	Right	Italian/ English	12	OR1: 11:4 OR2: 3:5	OR1: 11:4 OR2: 3:5	Oligodendroglioma Grade II
F022	1, 2, 3	63	63	Female	Right	English	16	4:0	4:0	Meningioma Grade II
F028	1, 2	74	74	Male	Right	English	13	50:0	50:0	Idiopathic epilepsy
F029	2, 3	38	38	Male	Right	English	12	4:8	4:8	Idiopathic epilepsy

(c) Bilateral lesions

Patient	Studies	Age	Gender	Handedness	First Language/ Tested	Education (years)	Time	Aetiology
F027	1, 2, 3	54	Female	Right	English	19	11:11	Meningioma Grade II

[1] 1: Frontal Assessment Battery; 2: Utilization Behaviour; 3: Context Retrieval Memory Task

Left-sided prefrontal lesions. Fourteen patients had their frontal lesion in the left hemisphere. It always spared Broca's area on the inferior frontal gyrus, except for two patients (F017 and F024), who suffered a cerebrovascular accident involving this region. They were not aphasic at the time of testing. The following section is a description of each individual left-sided frontal lesion. The available lesions are represented in Figures 1a to 1g.

F001. In this patient, the lateral frontopolar region (area 10) is completely removed, but sparing the orbitofrontal surface. There are also resections of the dorsolateral region (areas 9/46 & 46) extending on the dorsomedial surface, essentially the medial surface of the superior frontal gyrus (probably area 9). In addition, there might have been some damage to the ventrolateral area 45. However, posterior dorsolateral areas 6 and 8 and posterior ventrolateral area 44 appear intact.

F005. The excision includes the posterior part of the superior frontal gyrus that is just anterior to the precentral sulcus (area 6R). The superior precentral sulcus is spared at this level. The lesion continues ventrally on the posterior-most part of the middle frontal gyrus and includes the precentral gyrus and part of the postcentral gyrus below the superior precentral sulcus. It includes only the middle part of the precentral and postcentral gyri in the ventral-dorsal direction, as the most ventral part is also preserved. Medially, the lesion extends in front of the paracentral lobule to include the SMA as well as part of the cingulate sulcus, which would include at least one of the posterior cingulate motor areas.

F006. The left ventrolateral prefrontal cortex was resected in this patient. The lesion involves primarily the lateral orbital sulcus, the pars orbitalis and the

anterior part of pars triangularis (areas 47/12 and 45). The pars opercularis and the posterior half of the pars triangularis are spared. Even the posterior bank of triangular sulcus appears to be spared. Dorsally, the mid-dorsolateral area (area 46) is intact and so are the anterior and ventral orbitofrontal regions. The medial surface is all spared. Some of the tumour is not entirely removed and includes the anterior-most part of the insula and the lateral orbital gyrus.

F007. A large portion of the left anterior frontal cortex is resected in this patient. On the medial surface, the paracentral lobule and the supplementary motor areas are intact, as well as the cingulate regions just inferior to them. However, all the cortex and subjacent white matter anterior to the genu of the corpus callosum is removed, except the subcallosal gyrus (area 25). On the lateral surface, all the motor and premotor areas are intact, as well areas 8A and 8B and Broca's area. More specifically, the pars opercularis and the posterior part of the pars triangularis are intact, but the anterior part of the pars triangularis is damaged. The entire cortex anterior to those areas has been removed in the superior, middle and inferior frontal gyri and orbitofrontal region.

F008. On the lateral surface, the lesion includes the superior precentral sulcus and the cortex immediately anterior and posterior to it. Rostrally, the lesion comprises the posterior-most part of the cortex of the superior and middle frontal gyri and caudally, it continues on the precentral gyrus. This region corresponds to dorsal area 6. On the medial surface, the cortex immediately in front of the paracentral lobule is removed, therefore including the SMA and the most caudate cingulate motor area on the posterior bank of the cingulate sulcus. However, the

pre-SMA is intact, as well as the cingulate cortex and the two anterior cingulate motor areas.

F010. The resection was done in the posterior part of the middle frontal gyrus (entire area 8 and rostral area 6) and might also have extended a bit in the inferior part of the superior frontal gyrus. The lesion invades deeper into the subjacent white matter to include the portion of the corpus callosum just behind the genu. It seems to have disconnected the cingulate and adjacent medial area 8 from its inputs (see the coronal section and the shaded region on the medial view on Figure 1c). It may also have destroyed axons of the superior longitudinal fasciculus connecting the inferior parietal cortex to the mid-dorsolateral prefrontal area. However, the mid-dorsolateral is intact. The inferior frontal gyrus (pars orbitalis, triangularis and opercularis), the orbitofrontal region as well as the anterior part of the prefrontal cortex are all spared.

F012. In this patient, the surgical removal includes the most rostral part of the insula, the entire pars orbitalis (area 47/12) and more rostrally, the white mater of the anterior part of the pars triangularis, thus disconnecting the pars triangularis. The frontopolar, mid-dorsolateral, medial and orbital regions are all spared.

F017. This patient suffered a cerebrovascular accident in the left ventrolateral prefrontal cortex. The lesion comprises the inferior frontal gyrus from the horizontal ramus of the Sylvian fissure to the inferior precentral sulcus. It therefore includes the entire pars opercularis and pars triangularis, thus Broca's area. It extends a bit posteriorly on the anteriormost part of the precentral gyrus and dorsally in the adjacent middle frontal gyrus, more specifically on the inferior

part of Brodmann area 8A between the posterior middle frontal sulcus-posterior and the posterior middle frontal sulcus-intermediate.

F018. This patient's lesion includes primarily the SMA and the cortex anterior and ventral to it. It goes anteriorly to include the pre-SMA and extends as far as the level of the genu of the corpus callosum. Ventrally, the lesion involves the adjacent cingulate sulcus, probably affecting the 2 posterior cingulate motor areas, and the paracingulate gyrus, but it does not involve the cingulate gyrus per se. Finally, a little bit of the caudal part of the superior frontal gyrus is affected. The orbital, lateral and medial surfaces of the frontopolar region are intact, as well as the mid-dorsolateral and ventrolateral regions.

F021. In this patient, the left frontopolar (area 10) is removed on the lateral, medial and orbital surfaces. If there is damage to the mid-dorsolateral area, it is very mild and in its anteriormost part. The rest of the cortex is spared.

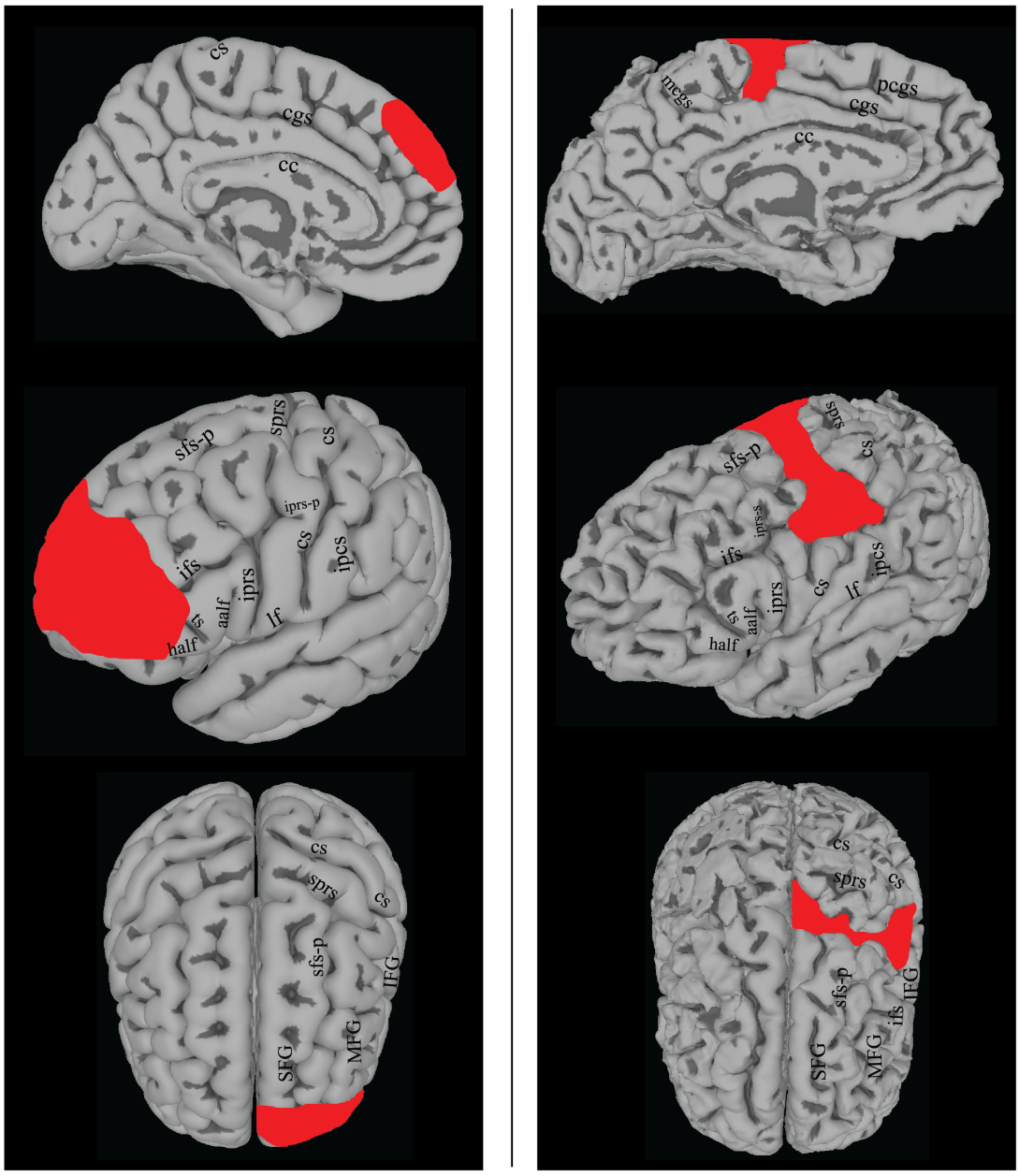
F023. The MRI scan was not available for this patient, but we received confirmation from her neurosurgeon that the excision was limited to the prefrontal cortex.

F024. This patient suffered a cerebrovascular accident in Broca's area (areas 44 & 45). It might have included a bit of rostral area 6. The adjacent mid-dorsolateral (areas 9/46&46) and frontopolar regions are intact. The medial and orbital surfaces also seem preserved.

F025. This patient had undergone removal of the left medial frontal cortex, with lesion in the SMA, pre-SMA, anterior part of cingulate and paracingulate cortex and medial part of the frontal lobe. In addition, the anterior

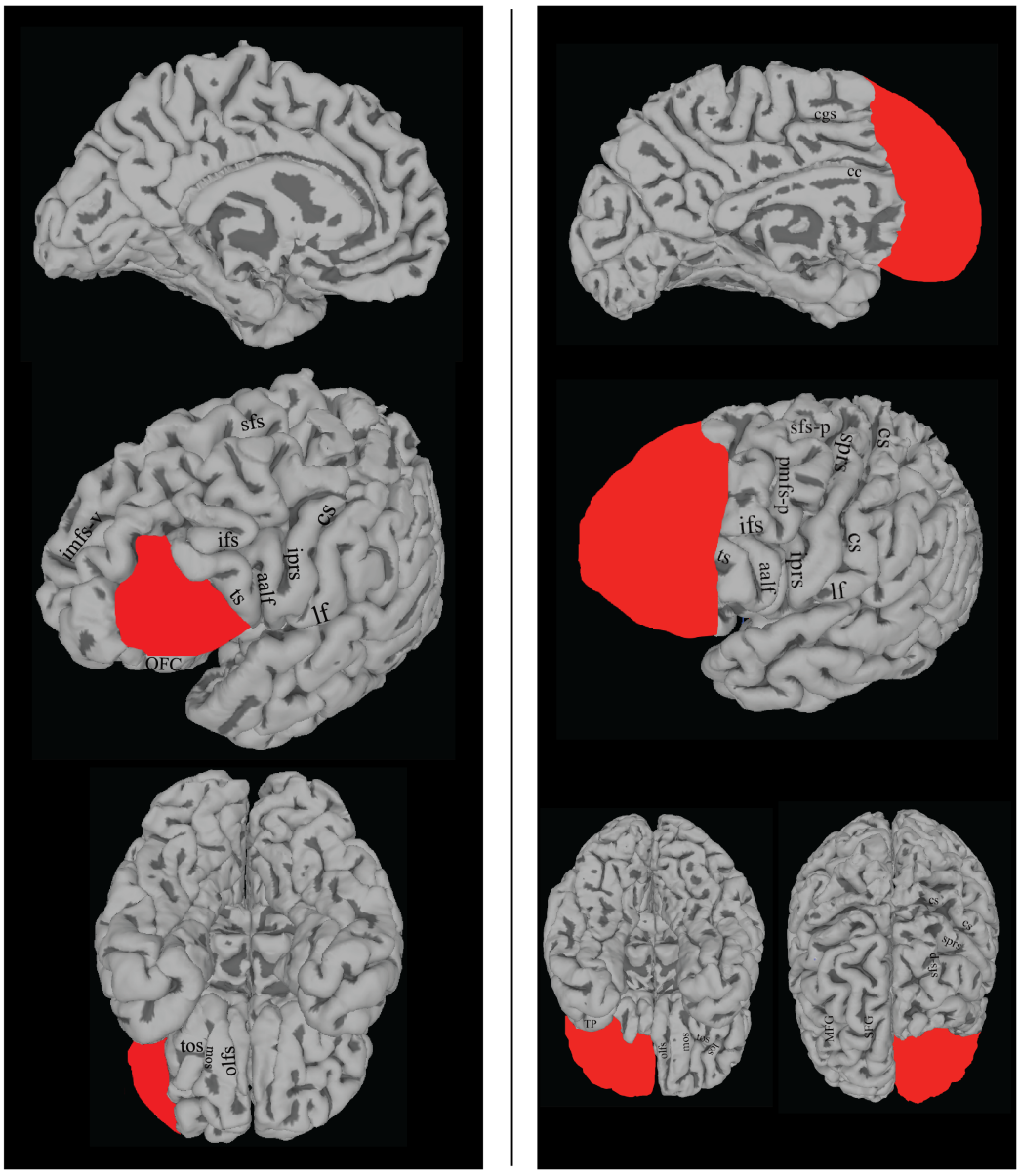
part of the body of corpus callosum, involved in the transfer of motor and premotor information, is also removed.

F026. This patient had a resection in the left dorsomedial frontal region, more specifically on the anterior part of the superior frontal gyrus. On the medial surface, the cortex anterior to the SMA is removed, including medial areas 8, 9 and 10 as well as the anterior part of paracingulate gyrus. The primary motor cortex, the SMA and the cingulate gyrus are all intact. On the lateral surface, the lesion includes the anterior part of the superior frontal gyrus, leaving the middle and inferior frontal gyri intact.



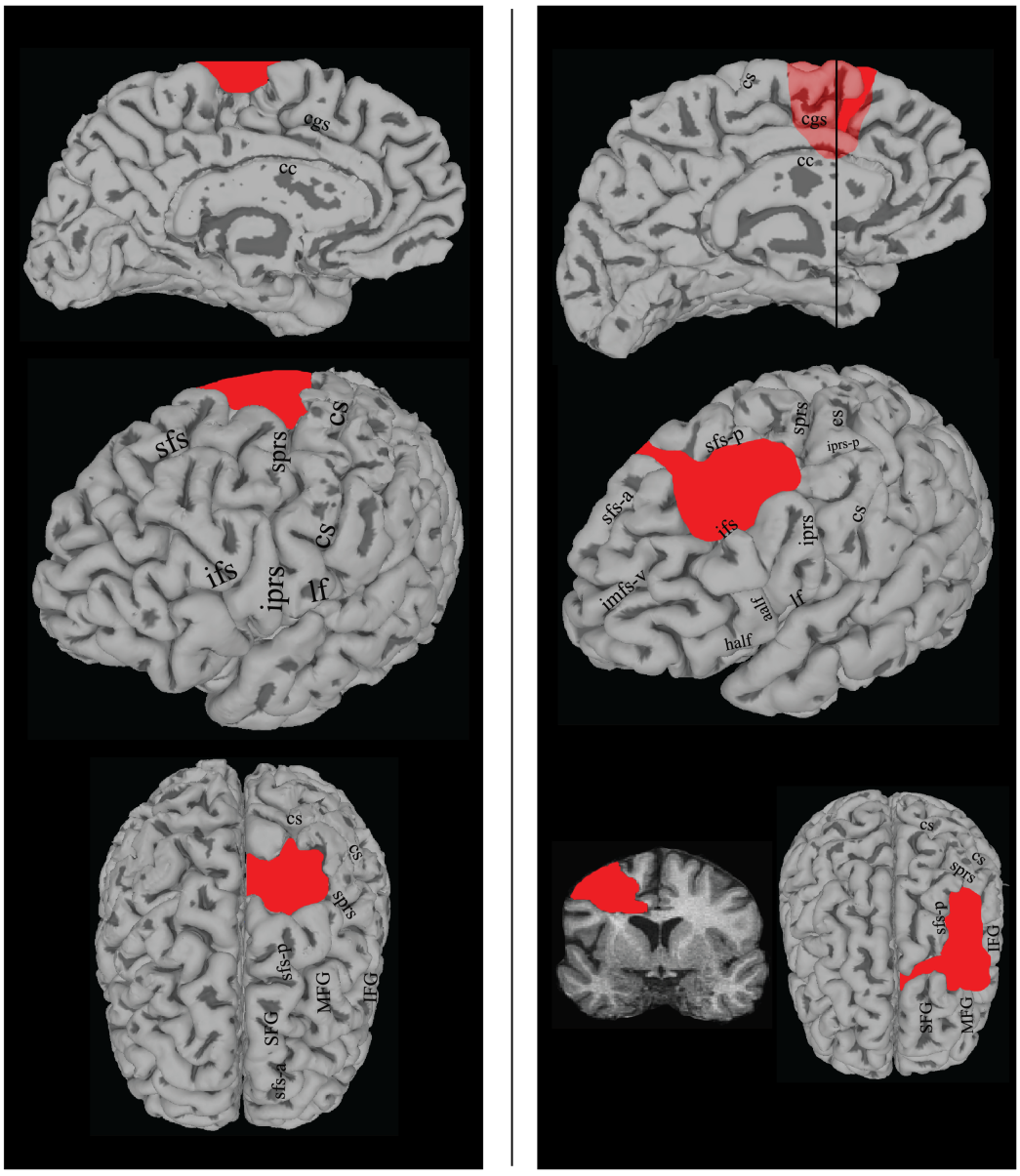
F001 F005

Figure 1a



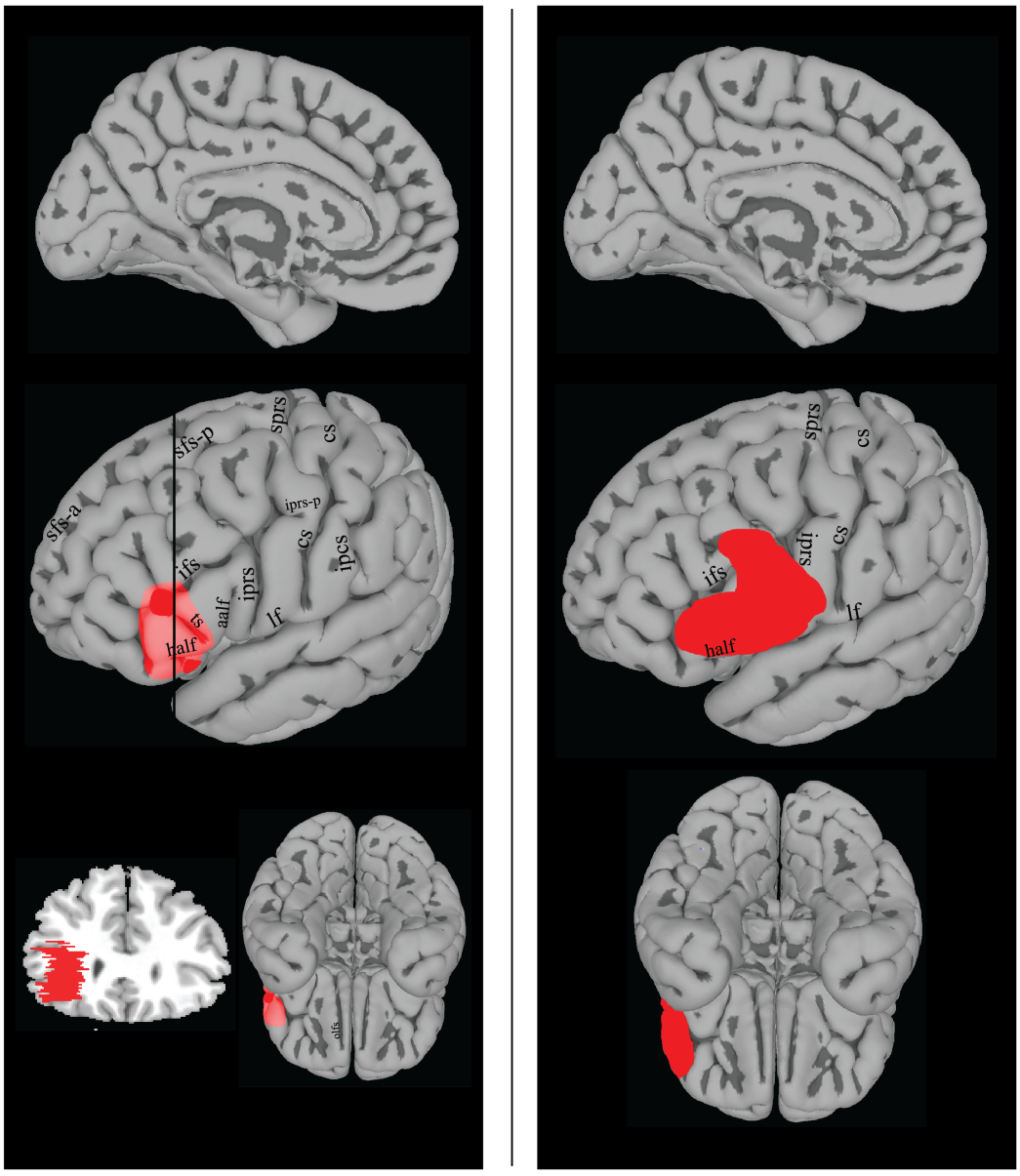
F006 F007

Figure 1b.



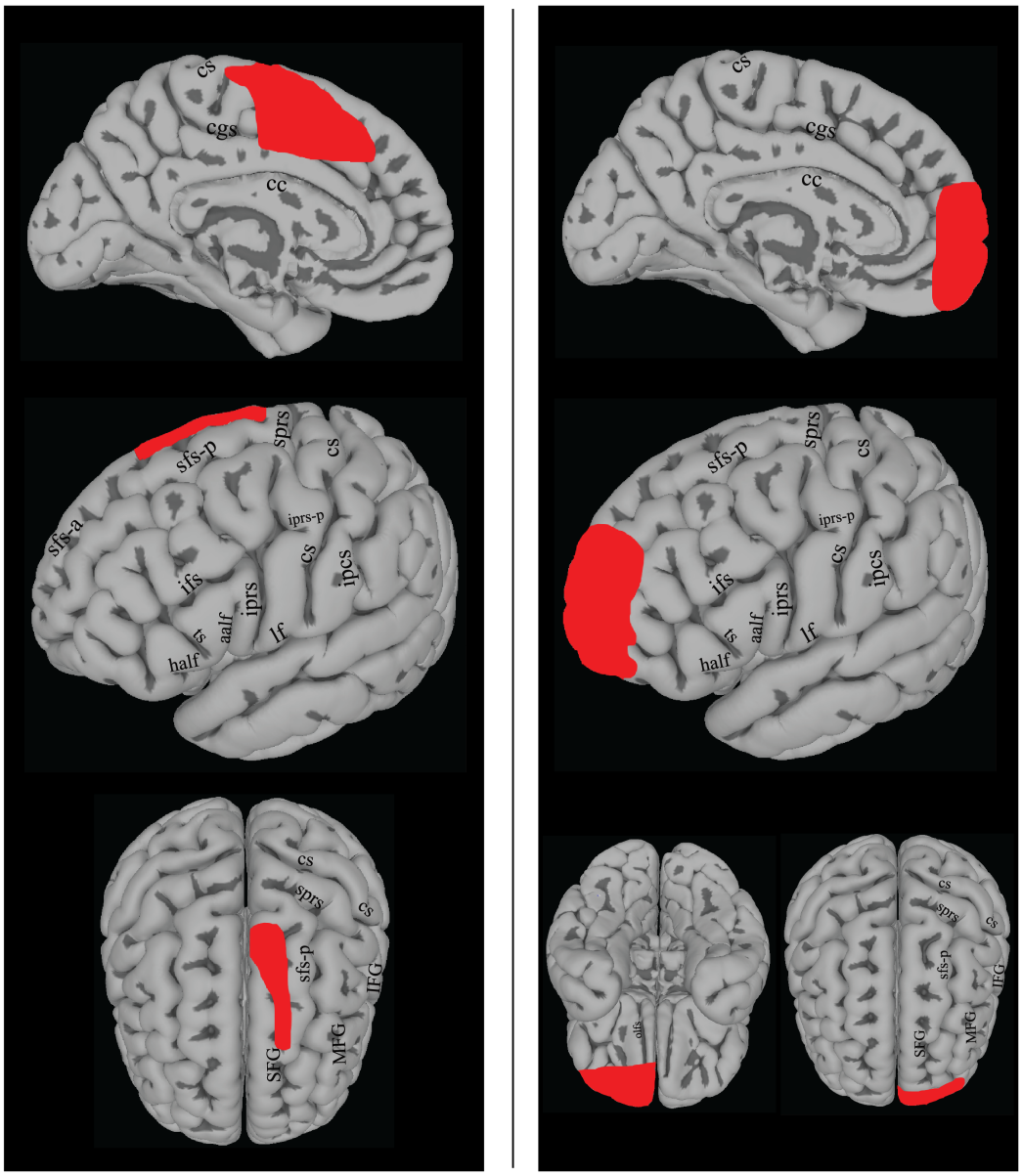
F008 F010

Figure 1c.



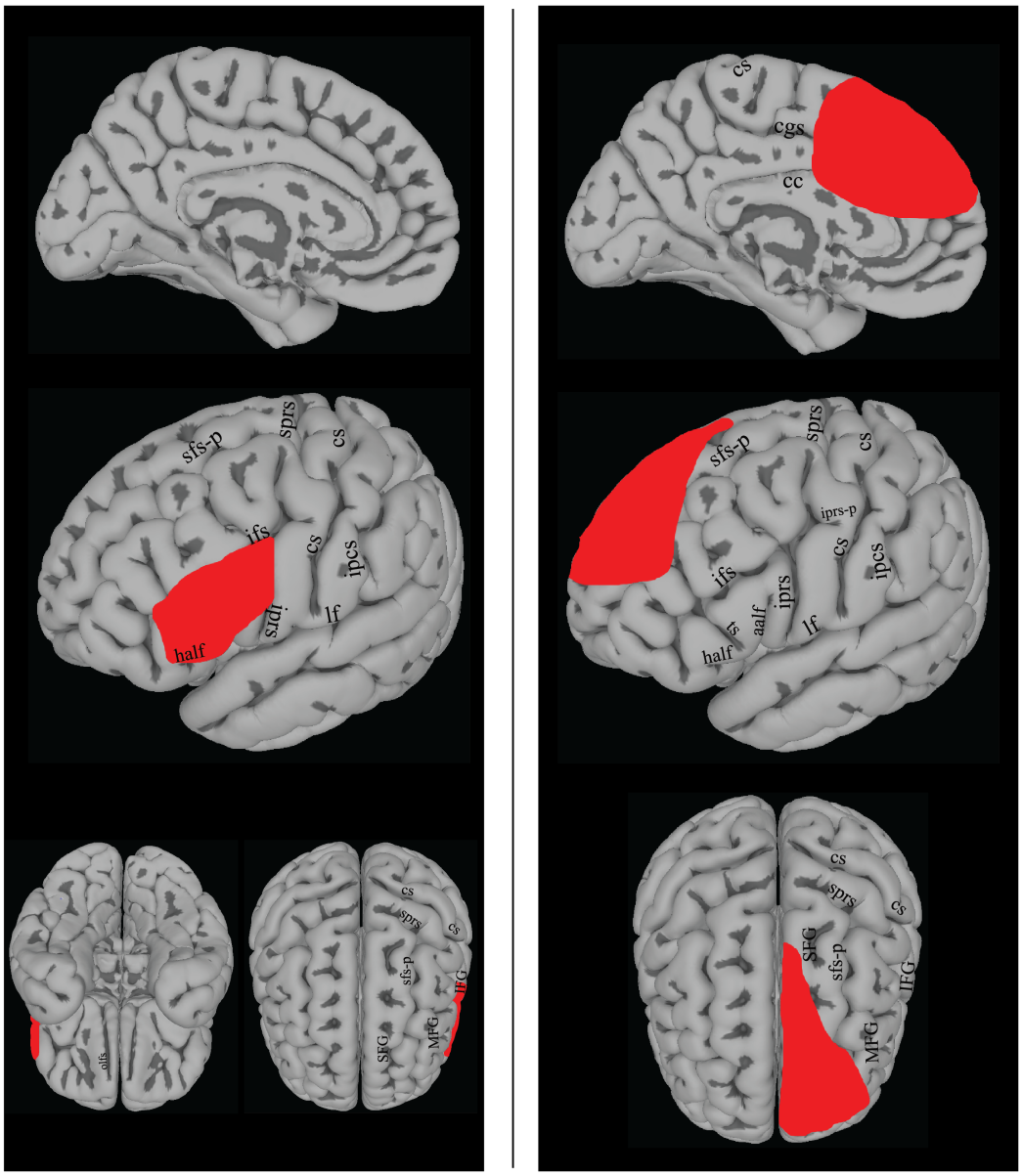
F012 F017

Figure 1d.



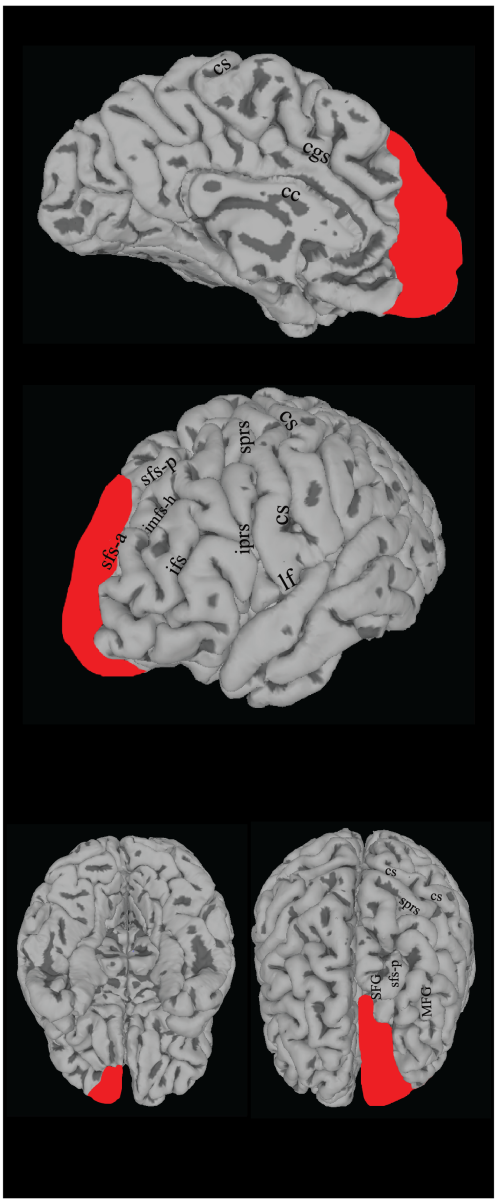
F018 F021

Figure 1e.



F024 F025

Figure 1f.



F026

Figure 1g.

Figure 1a-g. The cortical lesions (in red) of the patients with left frontal cortex lesions. The medial and lateral extents of the lesions are shown, as well as the ventral and dorsal views when relevant. The lesions are displayed on the 3D-reconstructions of the post-operative magnetic resonance images (MRI) for Patients F005, F006, F007, F008, F010 and F026; and on the standard Montreal Neurological Institute (MNI) brain for Patients F001, F012, F017, F018, F021, F024 and F025. In the latter cases, tracings of the lesions were used with MRIcro software (Rorden & Brett, 2000) to display them on the MNI brain. The anatomical data for Patient F023 were not available. Abbreviations: aalf = ascending anterior ramus of the lateral fissure; cc = corpus callosum; cgs = cingulate sulcus; cs = central sulcus; half = horizontal anterior ramus of the lateral fissure; IFG = inferior frontal gyrus; ifs = inferior frontal sulcus; imfs-h = intermediate middle frontal sulcus – horizontal; imfs-v = intermediate middle frontal sulcus – vertical; ipcs = inferior post-central sulcus; iprs = inferior precentral sulcus; iprs-p = inferior precentral sulcus – posterior; iprs-s = inferior precentral sulcus – superior; lf = lateral fissure; los = lateral orbital sulcus; mcgs = marginal branch of the cingulate sulcus; MFG = middle frontal gyrus; mos = medial orbital sulcus; OFC, orbitofrontal cortex; olfs = olfactory sulcus; pcgs = paracingulate sulcus; pmfs-p = posterior middle frontal sulcus - posterior; SFG = superior frontal gyrus; sfs = superior frontal sulcus; sfs-a = superior frontal sulcus – anterior; sfs-p = superior frontal sulcus – posterior; sprs = superior precentral sulcus; tos = transverse orbital sulcus; TP = temporal pole; ts = triangular sulcus.

Right-sided prefrontal lesions. Eleven patients had their frontal lesion in the right hemisphere. The following section is a description of each individual right-sided frontal lesion. The lesions are represented on Figures 2a to 2g when available.

F004. The right posterior ventrolateral areas 44 and 45 are resected in this patient with some possible extensions caudally in the ventral portion of the premotor area and rostrally into the frontopolar area 10 and a very small portion of area 9/46. Areas 8 and 9/46 are intact posteriorly. The lesion also extends on the posterior orbital surface.

F009. This is a case of large right prefrontal resection, including the entire frontopolar area 10 (lateral, medial and orbital surfaces), the orbitofrontal cortex, the ventrolateral prefrontal areas 44, 45 and 47/12 and the dorsolateral areas 46, 9/46 and 8 lying on the middle frontal gyrus. On the lateral surface, only the superior frontal and precentral gyri are spared. On the medial surface, the medial portion of the superior frontal gyrus and the cingulate gyrus also seem spared.

F011. The caudal-most part of the superior frontal gyrus just anterior to the superior precentral sulcus is removed. It includes the caudal half of the posterior-most superior frontal paramidline sulcus (i.e. superior part of area 6R). However, the anterior part of superior frontal gyrus is spared. The lesion continues on the posterior-most part of the middle fontal gyrus, including the cortex around the posterior middle frontal sulcus – posterior branch (pmfs-p) but it does not reach the posterior middle frontal sulcus - intermediate branch (pmfs-i). This means that at this level, there was a resection of 6R that may also have

invaded the posterior part of area 8A. The inferior frontal gyrus, the frontopolar, orbitofrontal regions and the precentral gyrus are all intact.

F014. This patient has a right posterior lateral prefrontal lesion, sparing the motor and premotor areas. Both the superior and inferior frontal gyri are intact. However, the posterior part of the middle frontal gyrus is removed in the territory of area 8. In addition to the cortex being resected, the lesion goes deeply into the white matter, suggesting the fibre tracts lying underneath have also been destroyed, leaving more anterior regions of the lateral prefrontal cortex disconnected from input to posterior regions.

F015. The MRI scan of this patient was not available. However, the operation report specifies that she underwent a corticectomy of the mid-SMA on the medial aspect of the superior frontal gyrus, extending 4 cm in the rostral-caudal axis and 2.5 cm in the dorsal-ventral axis.

F016. This lesion primarily involves the frontopolar region with the most anterior part of the lateral orbitofrontal region removed. However, the caudal portion of the orbitofrontal cortex is intact, as well as the rest of the prefrontal cortex.

F019. This patient suffered a cerebrovascular accident in the right orbitofrontal region. The lesion extends from the lateral part of the medial orbital gyrus to the lateral orbital sulcus. The cortex surrounding the olfactory sulcus is all spared (gyrus rectus and medial part of the medial orbital gyrus). Even though the medial aspect of the orbitofrontal region is intact, the lesion extends onto the medial surface at the level of the genu of the corpus callosum. The dorsomedial and lateral prefrontal cortex is all spared.

F020. This resection involves the ventral and inferior dorsal aspect of the right lateral prefrontal cortex. The lesion extends from the inferior precentral sulcus (with possible small damage in the precentral gyrus) to the lateral frontopolar area 10. Therefore, areas 44, 45 and 47/12 are all removed. Dorsally, the lesion extends into the mid-dorsolateral areas 46 and 9/46 on the middle frontal gyrus. The lateral part of the orbitofrontal cortex is resected up to the lateral orbital sulcus posteriorly, but extending into the anterior orbital gyrus anteriorly. The medial surface is all intact.

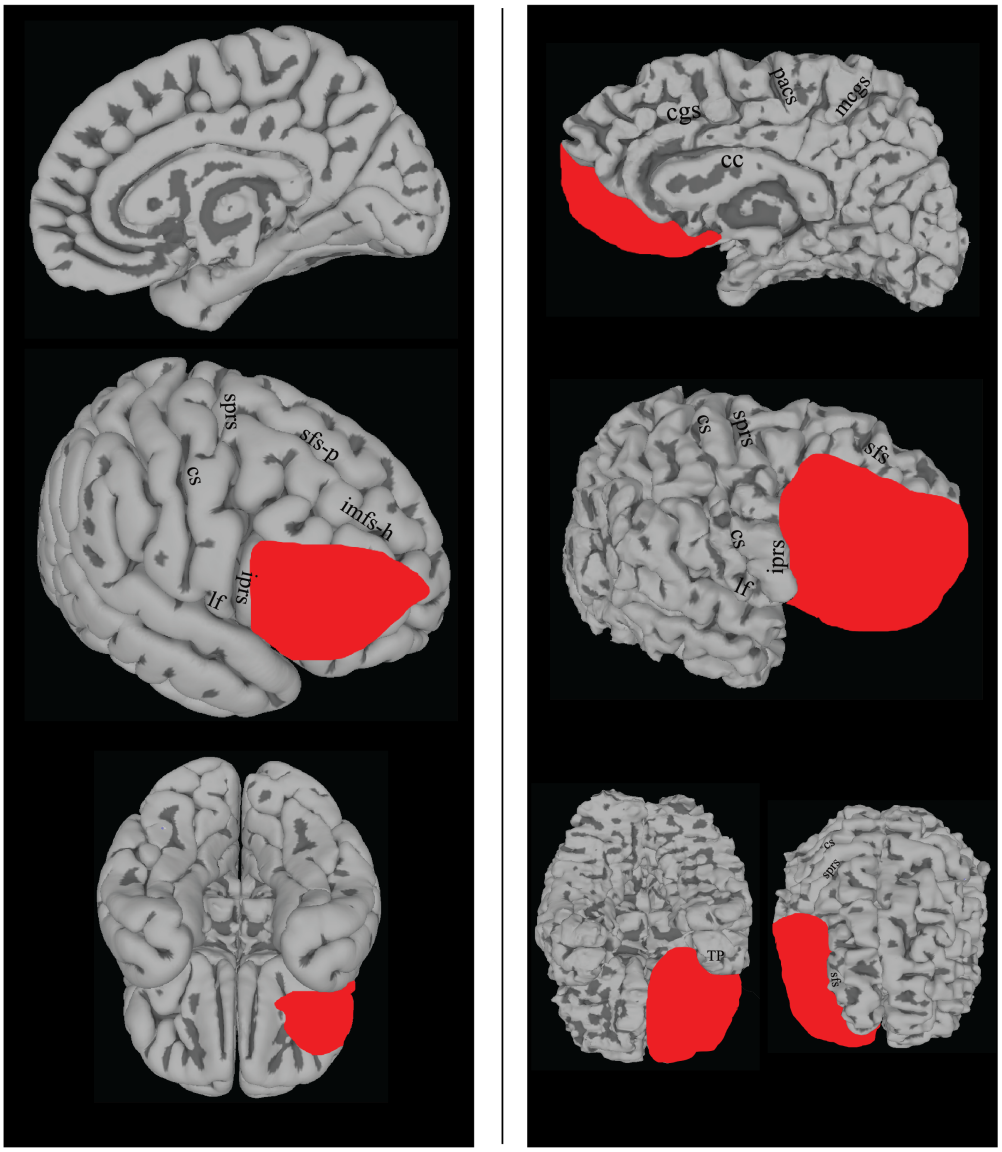
F022. The MRI scan was not available for this patient, but we received confirmation from her neurosurgeon that the excision was limited to the prefrontal cortex.

F028. The entire right prefrontal cortex of this patient was removed starting at the level of the precentral sulcus. The lateral, orbital and medial cortical surfaces as well as the immediately underlying white matter are removed, with the exception of the corpus callosum.

F029. The MRI scan was not available for this patient, but we received confirmation from his neurosurgeon that the excision was limited to the prefrontal cortex.

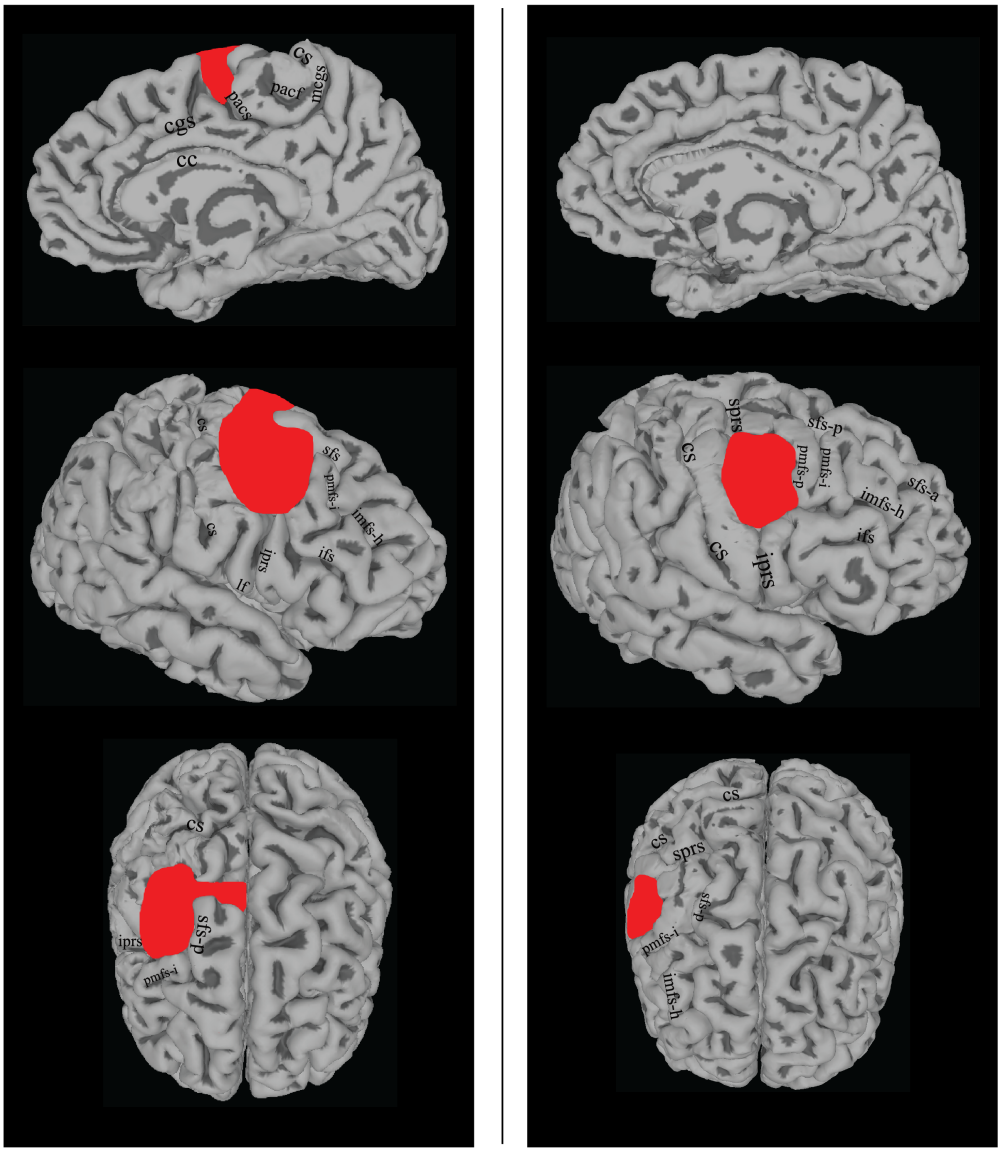
Bilateral prefrontal lesions.

F027. This patient has a small lesion involving the most dorsal part of SMA bilaterally. The cortex around and posterior to the medial precentral sulcus and the paracentral lobule (i.e. area 4) are all intact. There is no damage to the cingulate region.



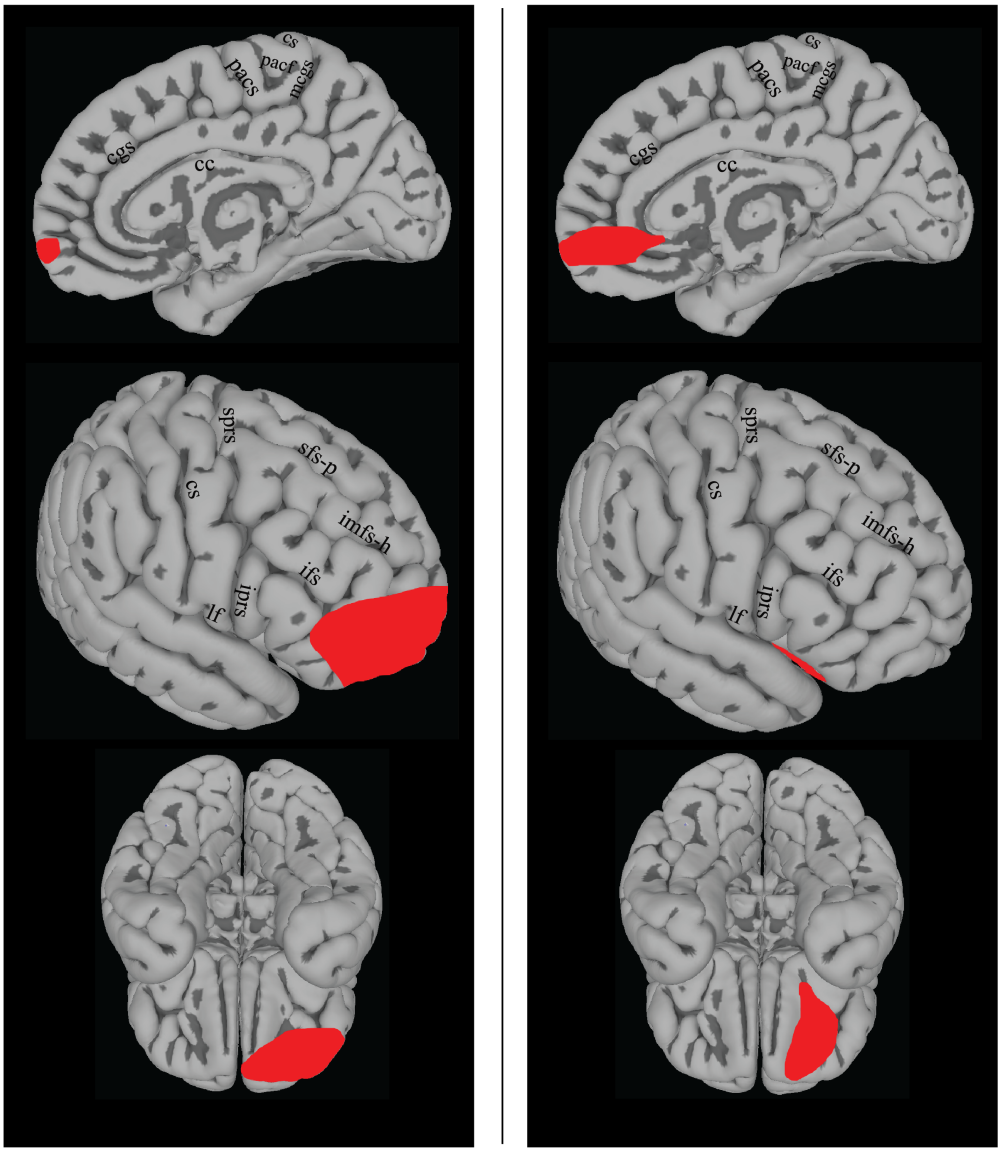
F004 F009

Figure 2a.



F011 F014

Figure 2b.


cs
pacs
pacf
mcgs
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sfs-p
cs
imfs-h
ifs
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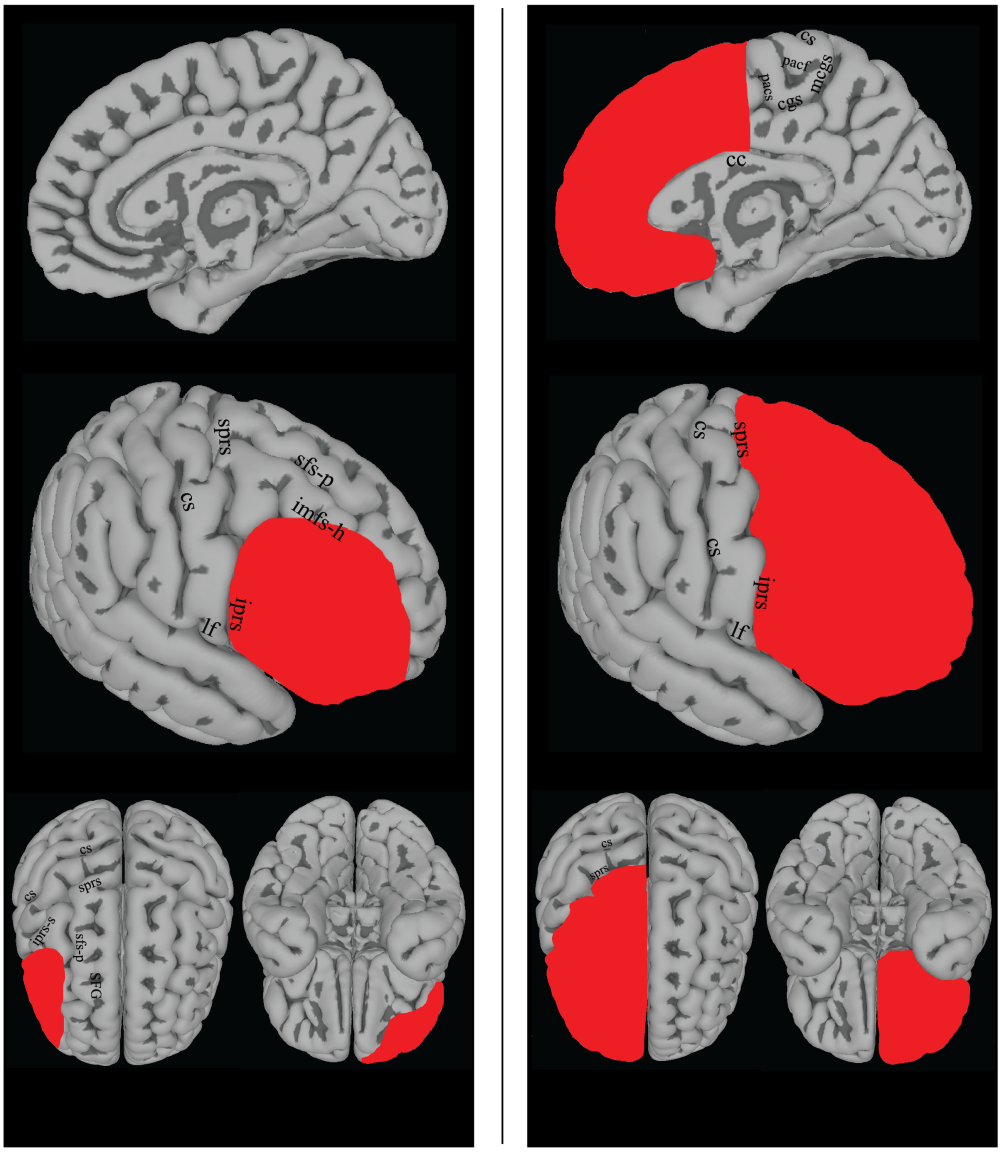
lf
F016
F019

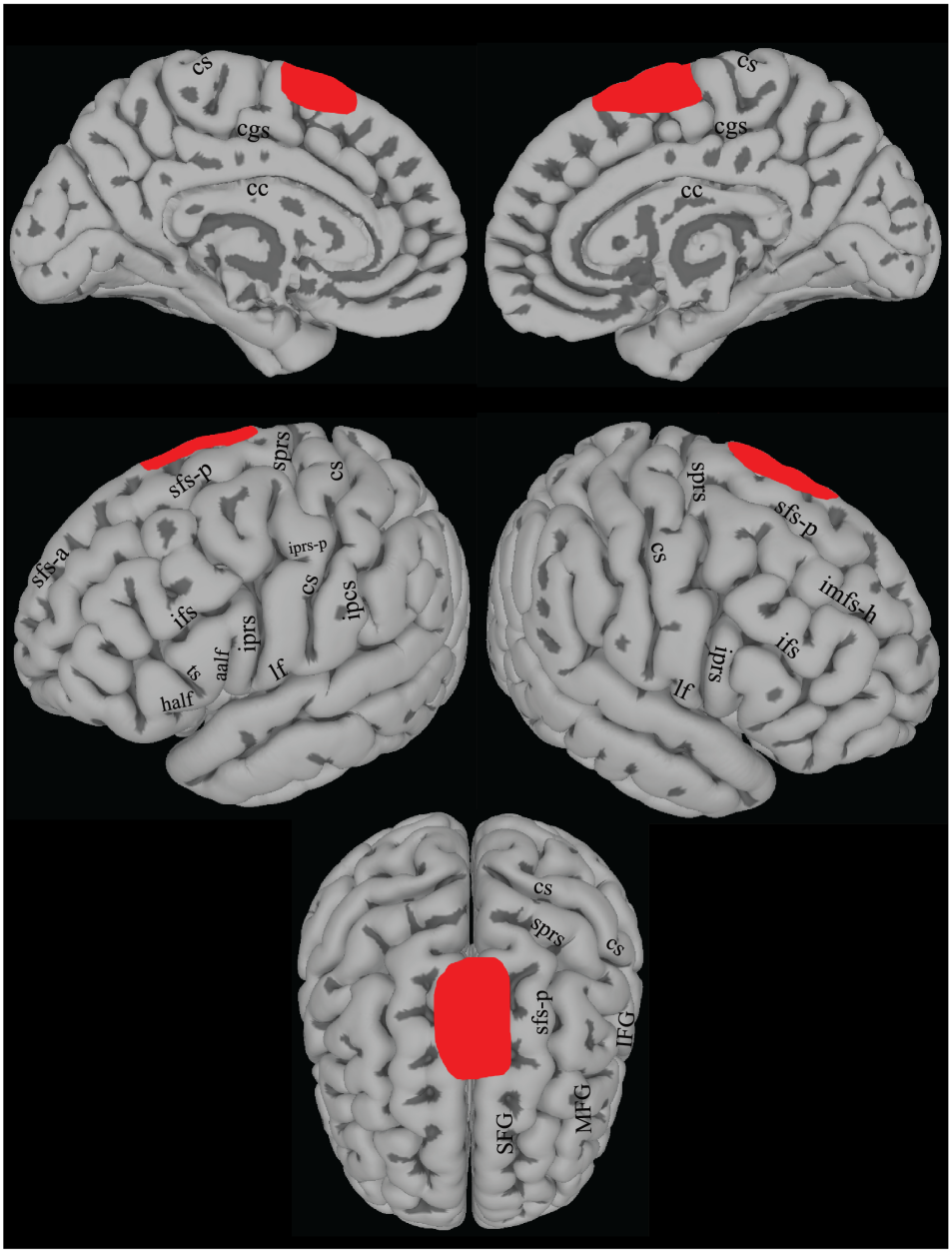
Figure 2c.



F020 F028

Figure 2d.

Figure 2a-d. The cortical lesions (in red) of the patients with right frontal cortex lesions whose anatomical data were available. The medial and lateral extents of the lesions are shown, as well as the ventral and dorsal views when relevant. The lesions are displayed on the 3D-reconstructions of the post-operative MRI for cases F009, F011 and F014 and on the standard MNI brain for cases F004, F016, F019, F020 and F028. In the latter cases, tracings of the lesion were used with MRIcro software (Rorden & Brett, 2000) to display them on the MNI brain. The anatomical data for Patients F015, F022 and F029 was not available. See Fig. 1a-g for label abbreviations. pacf = paracentral fissure; pacs = paracentral sulcus; pmfs-i = posterior middle frontal sulcus - intermediate.



F027

Figure 3.

Figure 3. The cortical lesions (in red) of the bilateral frontal patient F027. The medial, lateral and dorsal extents of the lesions are shown. The lesions are displayed on the standard MNI brain using MRIcro software (Rorden & Brett, 2000). See Fig. 1a-g for label abbreviations.

Patients with temporal lobe lesions

Twenty patients with lesions restricted to the temporal lobe were included. Each patient in the temporal group was matched as closely as possible with one patient in the frontal group for age and education. Twelve of the temporal lesions were left-sided and eight were right-sided. Eight of the patients with temporal lesions had undergone neurosurgery for the removal of epileptogenic tissue (three left- and five right-sided excisions), 11 for the removal of a tumour (eight left- and three right-sided lesions) and one patient with left-sided lesion had suffered a cerebrovascular accident. The eight surgical removals of epileptogenic tissue and six of the eleven tumour removals involved either a selective amygdalo-hippocampectomy, in which the two medial temporal structures are resected with the surrounding neocortex, or a resection of the anterior temporal cortex including the amygdala and the anterior part of the hippocampal formation (see detailed description below). The anatomical data for the remaining six temporal lesions were not available, but there was confirmation from the neurosurgeon or neurologist that the lesion did not extend outside the temporal lobe. Characteristics of the patients with left and right temporal lobe lesions are presented in Table 2a and 2b, respectively. The lesions whose post-operative MRI or tracings were available are presented in Figures 4a to 4c.

Table 2. Characteristics of patients with temporal lobe lesions

(a) Left-sided lesions

Patient	Studies[1]	Age for 1, 3	Age for 2	Gender	Handedness	First Language/ Tested	Education (years)	Time for 1, 3	Time for 2	Aetiology
T003	1, 2, 3	62	64	Female	Ambidextrous	French	19	5:8	8:4	Desembryoplastic neuro-epithelial tumour
T004	1, 2, 3	20	22	Male	Right	French	16	1:4	3:5	Desembryoplastic neuro-epithelial tumour
T005	1, 2, 3	43	45	Male	Right	French	15	2:6	4:1	Idiopathic epilepsy
T006	1, 3	37	-	Male	Right	French	17	1:7	-	Glioma Grade II
T007	1, 2, 3	52	54	Male	Right	French	12	11:10	13:5	Epilepsy
T008	1, 2, 3	39	39	Male	Right	French	17	2:2	2:2	Astrocytoma Grade II
T009	1, 2, 3	38	38	Female	Right	English	18	4:5	4:5	Epilepsy
T010	1, 3	45	-	Male	Right	French	16	4:2	-	Stroke
T014	1, 2, 3	48	48	Male	Right	French	12	0:10	0:10	Oligoastrocytoma Grade III
T016	1, 2, 3	61	61	Male	Right	Vietnamese/ French	16	23:0	23:0	Glioma Grade I
T017	1, 2, 3	52	52	Female	Right	French	13	OR1: 1:6 OR2: 0:6	OR1: 1:6 OR2: 0:6	Idiopathic epilepsy
T021	1, 2, 3	36	36	Female	Right	French	16	OR1: 11:5 OR2: 8:1	OR1: 11:5 OR2: 8:1	Oligodendroglioma Grade II

[1] 1: Frontal Assessment Battery; 2: Utilization Behaviour; 3: Context Retrieval Memory Task

(b) Right-sided lesions

Patient	Studies[1]	Age	Gender	Handedness	First Language/ Tested	Education (years)	Time	Aetiology
T002	1	27	Male	Right	Spanish/ French	15	2:5	Idiopathic epilepsy
T011	1, 2, 3	59	Male	Right	French	16	0:11	Glioblastoma
T012	1, 2, 3	47	Female	Right	English	16	2:5	Endodermal cyst
T015	1, 2, 3	54	Male	Right	French	16	OR1: 0:9 OR2: 0:4	Astrocytoma Grade III
T018	1, 3	57	Female	Right converted	English	11	OR1: 32:1 OR2: 26:2	Idiopathic epilepsy
T019	1, 2, 3	60	Male	Right	French	16	16:6	Idiopathic epilepsy
T020	1, 2, 3	48	Male	Right	English	13	2:9	Idiopathic epilepsy
T022	1, 2, 3	51	Female	Right	French	14	17:6	Idiopathic epilepsy

[1] 1: Frontal Assessment Battery; 2: Utilization Behaviour; 3: Context Retrieval Memory Task

Left-sided temporal lesions.

T003. This patient underwent a left anterior temporal lobectomy with the resection extending a bit posteriorly in the middle temporal gyrus.

T004. This patient had a desembryoplastic neuro-epithelial tumour of 2.5 cm centered on the anterior part of the hippocampus and slightly extending on the posterior portion of the uncus and amygdala. The tumour was partially resected, only the superior and medial most part could not be removed.

T005. This patient had a standard left selective amygdalo-hippocampectomy.

T006. This patient underwent a left anterior temporal lobectomy.

T007. This patient underwent an anterior temporal lobe resection. The MRI scan of this patient (see Figure 4b) shows that the whole temporal lobe in front of the central sulcus is removed. Medially, the anterior collateral (human rhinal) sulcus is completely removed, but the posterior collateral sulcus is spared. Therefore, temporal part of the pyriform cortex, most of entorhinal cortex, the amygdala and the anterior part of the hippocampus are removed. The parahippocampal cortex and its subjacent hippocampus are intact.

T008. This patient's lesion consists of a removal of about 5.5 cm of the anterior left temporal lobe. The lateral, inferior and medial surfaces are all removed, including the amygdala and anterior part of the hippocampus buried in the lobe. According to the medical file, there was still some tumour posteriorly growing up into the stem of the temporal lobe that could not be resected.

T009. This patient underwent a standard left selective amygdalo-hippocampectomy.

T010. This patient suffered a cerebrovascular accident resulting in a lesion restricted to the temporal lobe as confirmed by a neurologist who reviewed his file. The precise location and extent of the lesion was not available.

T016. This patient sustained a lateral temporal lesion on the posterior third of the inferior temporal gyrus. Rostrally, the excision extends slightly on the middle temporal gyrus. The lesion also invades deeper into the white matter underlying the cortical excision.

T017. There was resection of 1 cm in the anterior third of the left hippocampus in this patient.

T014 and T021. The anatomical data were not available for these cases, but there was confirmation from the neurosurgeon that the lesions did not extend outside the temporal lobe.

Right-sided temporal lesions.

T002. This patient underwent a right selective amygdalo-hippocampectomy.

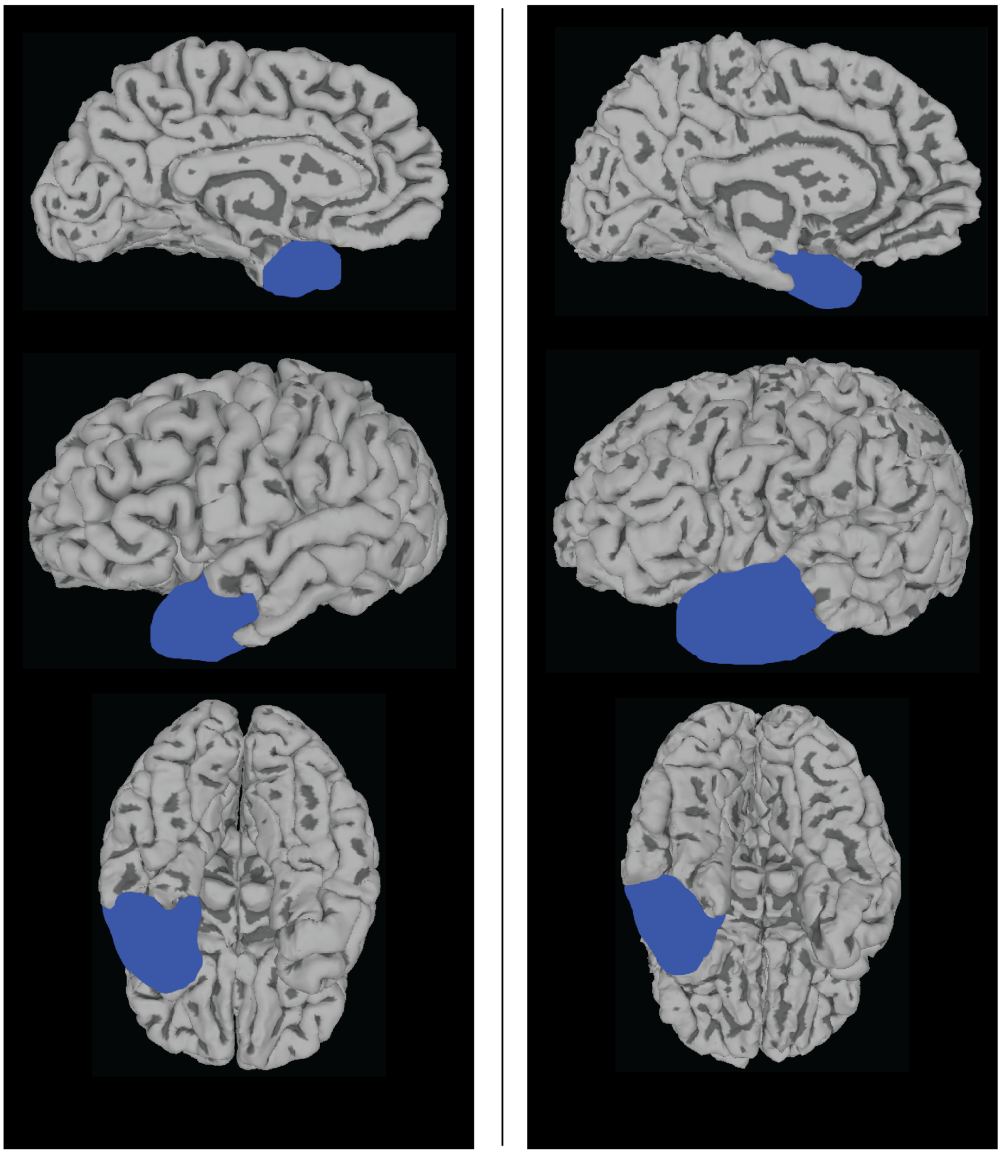
T018. In the first procedure, this patient underwent a standard right anterior temporal lobectomy. A second surgery was carried out to resect more tissue from the residual medial structures (amygdala, hippocampus, uncus and parahippocampal gyrus) and to extend the removal posteriorly to include almost the entire right temporal lobe.

T019. This patient underwent a right selective amygdalo-hippocampectomy.

T020. This patient underwent a right selective transcortical amygdalo-hippocampectomy

T022. This patient underwent a selective transcortical amygdalo-hippocampectomy. The excision includes 4/5 of the total volume of the amygdala, the entire uncus, an extent of 3.5 cm of the parahippocampus and 3 cm of the hippocampus.

T011, T012 and T015. The anatomical data were not available for these three cases, but there was confirmation from the neurosurgeon that the lesions were restricted to the temporal lobe.



T003 T006

Figure 4a.

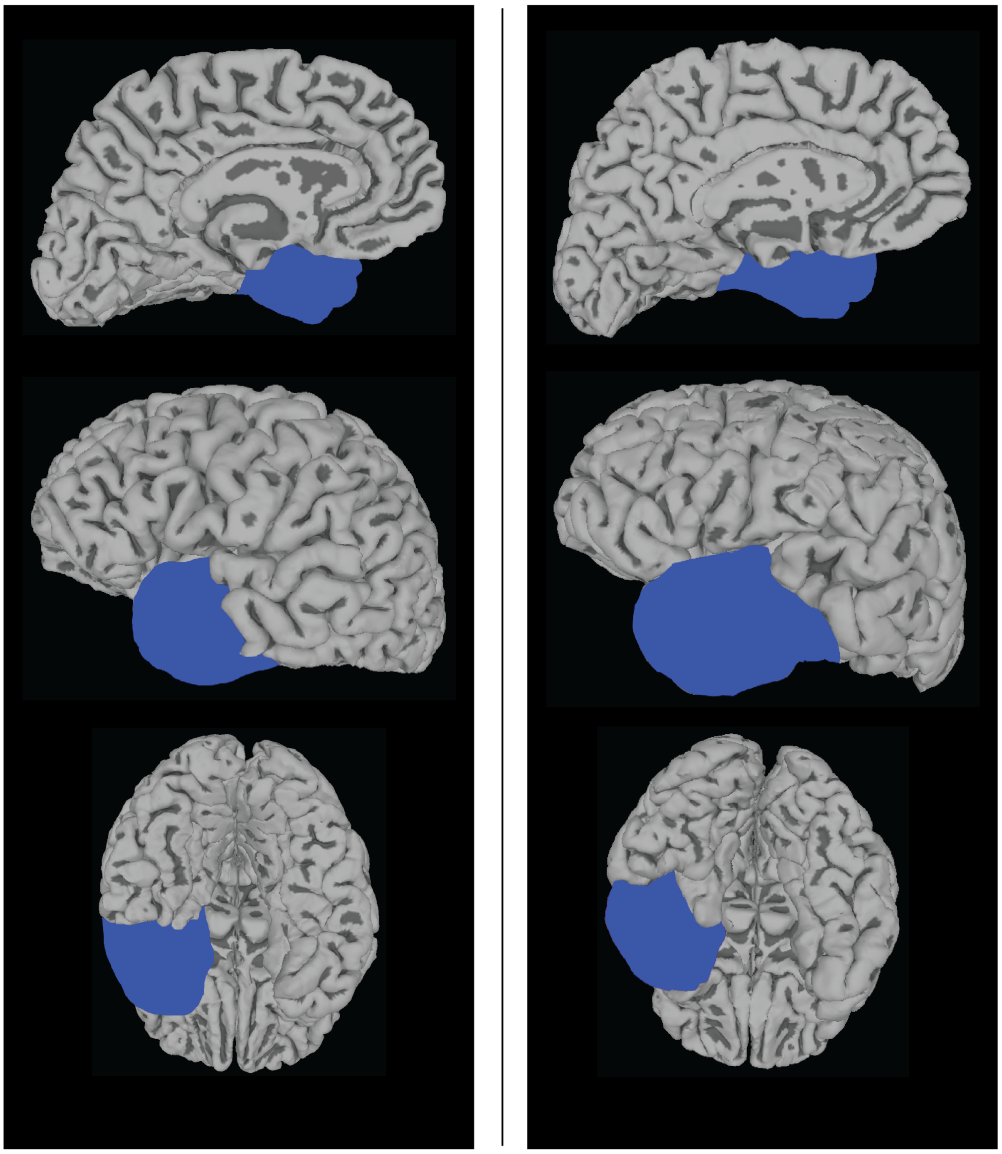
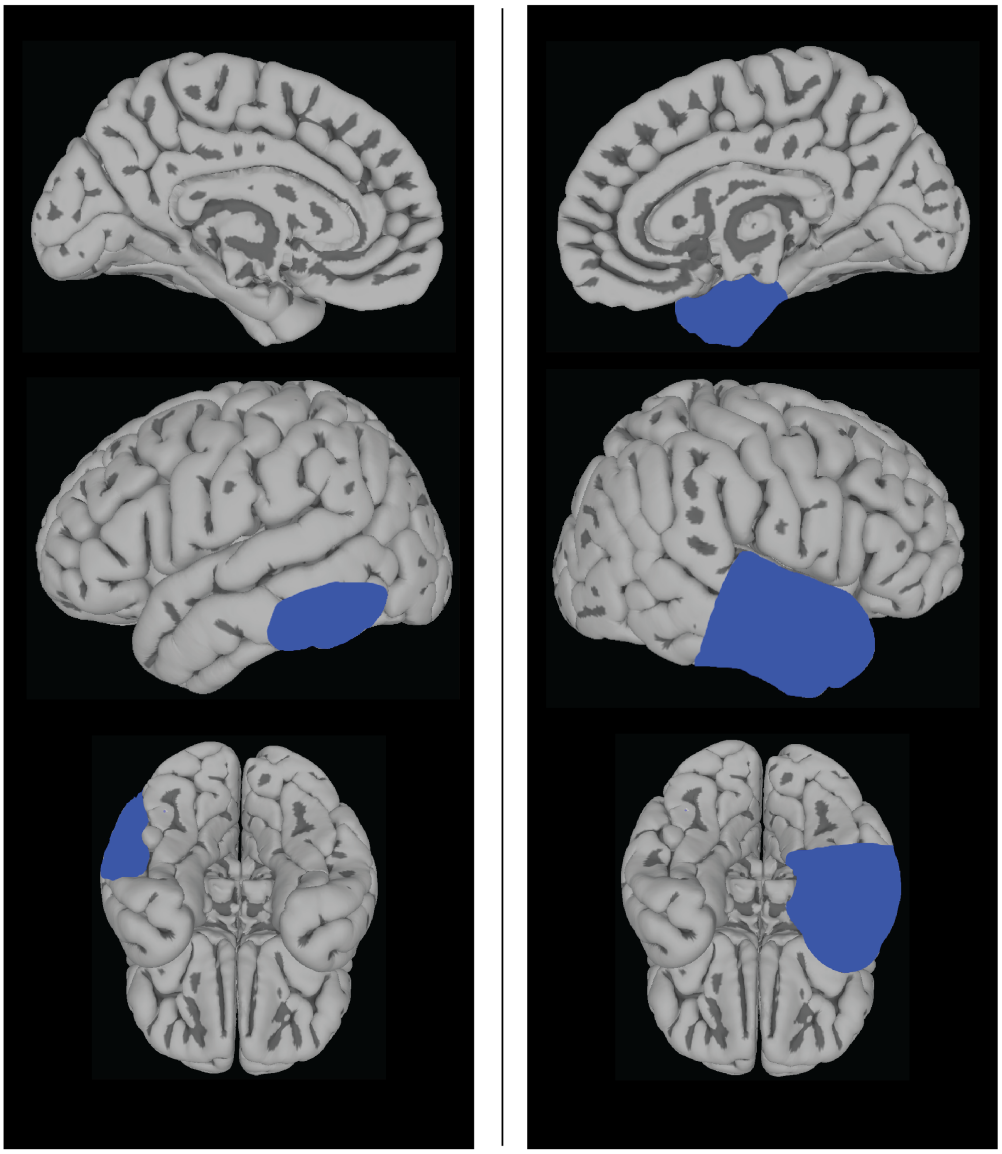


Figure 4b.



T016 T018

Figure 4c.

Figures 4a-c. The lesions (in blue) of patients with temporal lobe lesions. The medial, lateral and ventral extents of the lesions are shown. The lesions are displayed on the 3D-reconstructions of the post-operative magnetic resonance images (MRI) for Patients T003, T006, T007 and T008; and on the MNI brain for Patients T016 and T018. In the latter cases, tracings of the lesions were used with MRIcro software (Rorden & Brett, 2000) to display them on the MNI brain. The anatomical images for the other patients with temporal lobe damage were not available.

Healthy control participants

A group of neurologically healthy control participants was also included. In total, 26 subjects participated in at least two of the three studies. They were individuals with no history of traumatic brain injury, or of neurological or psychiatric disorder recruited among relatives of patients or in the McGill University community. Each control subject was matched as closely as possible with the one patient in the frontal group and one patient in the temporal group for age and education.

Standardized neuropsychological tests

All participants were administered a short battery of standard neuropsychological tests as part of their participation in the study. The Logical Memory (Stories) and Faces subtests of the Wechsler Memory Scale-III (WMS-III) and the California Verbal Learning Test – second edition (CVLT-II) were administered in order to obtain independent measures of verbal and non-verbal memory performance in participants. Attention and working memory were assessed with digit span forward and backward. For a standard measure of intelligence, the Wechsler Abbreviated Scale of Intelligence (WASI) was administered. Tables 3, 4 and 5 show the individual test scores for patients with frontal cortex lesions, patients with temporal lobe lesions and healthy control participants, respectively.

Table 3. Standard neuropsychological test results of patients with frontal cortex lesions

(a) Left-sided lesions

Subject	Memory									
	WMS LM imm (max 75)	WMS LM del (max 50)	WMS LM reco (/30)	WMS Faces imm (/48)	WMS Faces del (/48)	CVLT-II Learning Total (max 80)	CVLT-II Uncued imm (max 16)	CVLT-II Uncued del (max 16)	CVLT-II reco hits (/16)	CVLT-II false reco
F001	46	27	28	36	36	41	10	10	14	2
F005	50	32	28	36	33	NA	NA	NA	NA	NA
F006	58	38	27	36	35	62	13	15	16	0
F007	53	30	30	37	38	61	12	13	16	1
F008	48	29	27	38	37	NA	NA	NA	NA	NA
F010	56	34	29	46	43	NA	NA	NA	NA	NA
F012	41	25	25	44	42	NA	NA	NA	NA	NA
F017	52	24	26	38	33	46	9	12	13	1
F018	46	26	25	31	28	63	12	12	16	1
F021	62	41	29	39	38	72	16	16	16	0
F023	46	27	25	32	36	43	10	10	13	0
F024	46	28	26	40	37	68	13	14	16	0
F025	32	6	NA	28	35	25	2	1	12	9
F026	51	32	28	38	39	44	9	12	15	0

(a) Left-sided lesions (cont'd)

Subject	WASI FSIQ	Digit Span forward	Digit Span backward
F001	104	6	7
F005	116	5	5
F006	107	6	6
F007	118	6	6
F008	113	5	6
F010	124	7	5
F012	99	7	5
F017	84	5	4
F018	120	7	4
F021	131	8	7
F023	119	8	5
F024	98	7	3
F025	102	5	4
F026	96	6	5

(b) Right-sided and bilateral lesions

Subject	Memory									
	WMS LM imm (max 75)	WMS LM del (max 50)	WMS LM reco (/30)	WMS Faces imm (/48)	WMS Faces del (/48)	CVLT-II Learning Total (max 80)	CVLT-II Uncued imm (max 16)	CVLT-II Uncued del (max 16)	CVLT-II reco hits (/16)	CVLT-II false reco
F004	52	33	29	33	33	70	15	16	16	0
F009	33	20	NA	31	8	57	11	12	16	1
F011	53	29	26	36	36	NA	NA	NA	NA	NA
F014	51	36	29	44	44	68	15	16	16	0
F015	47	31	27	47	41	65	16	16	16	0
F016	51	35	30	45	42	72	16	14	16	0
F019	46	27	29	47	43	59	15	15	16	0
F020	52	34	25	39	39	55	13	13	15	1
F022	58	38	30	39	36	74	16	16	16	0
F028	48	27	26	33	28	NA	NA	NA	NA	NA
F029	34	22	19	36	32	NA	NA	NA	NA	NA
F027	55	38	30	45	40	72	16	16	16	0

(b) Right-sided and bilateral lesions (cont'd)

Subject	WASI FSIQ	Digit Span forward	Digit Span backward
F004	119	7	5
F009	84	5	4
F011	112	7	NA
F014	107	8	4
F015	95	8	6
F016	122	6	4
F019	120	6	3
F020	NA	5	4
F022	125	7	7
F028	113	6	4
F029	79	5	3
F027	121	8	7

Abbreviations: CVLT-II, California Verbal Learning Test – second edition; del, delayed; FSIQ, Full Scale Intelligence Quotient; imm, immediate; LM, Logical Memory (Stories); reco, recognition; WASI, Wechsler Abbreviated Scale of Intelligence; WMS, Wechsler Memory Scale-III.

Table 4. Standard neuropsychological test results of patients with temporal lobe lesions

(a) Left-sided lesions

Subject	Memory									
	WMS LM imm (max 75)	WMS LM del (max 50)	WMS LM reco (/30)	WMS Faces imm (/48)	WMS Faces del (/48)	CVLT-II Learning Total (max 80)	CVLT-II Uncued imm (max 16)	CVLT-II Uncued del (max 16)	CVLT-II reco hits (/16)	CVLT-II false reco
T003	57	37	29	44	44	61	15	16	16	0
T004	57	33	28	43	41	61	11	12	16	1
T005	34	18	25	NA	NA	40	7	7	8	12
T006	29	17	NA	36	42	NA	NA	NA	NA	NA
T007	39	22	24	34	32	39	6	10	15	3
T008	42	32	NA	42	40	71	16	13	16	0
T009	39	21	24	37	38	66	15	16	16	0
T010	43	28	26	36	37	61	11	13	16	1
T014	57	35	28	40	41	71	14	13	16	0
T016	45	23	23	28	28	47	9	11	13	1
T017	35	16	25	26	31	38	5	4	15	10
T021	43	21	28	NA	NA	67	13	15	16	1

(a) Left-sided lesions (cont'd)

Subject	WASI FSIQ	Digit Span forward	Digit Span backward
T003	127	8	5
T004	114	7	8
T005	120	9	7
T006	100	7	6
T007	103	6	8
T008	128	7	5
T009	97	8	5
T010	NA	8	8
T014	109	7	5
T016	106	8	5
T017	96	7	4
T021	85	7	7

(b) Right-sided lesions

Subject	Memory									
	WMS LM imm (max 75)	WMS LM del (max 50)	WMS LM reco (/30)	WMS Faces imm (/48)	WMS Faces del (/48)	CVLT-II Learning Total (max 80)	CVLT-II Uncued imm (max 16)	CVLT-II Uncued del (max 16)	CVLT-II reco hits (/16)	CVLT-II false reco
T002	45	28	28	43	42	NA	NA	NA	NA	NA
T011	48	20	26	29	35	52	12	10	14	1
T012	36	22	23	34	39	76	13	13	16	3
T015	52	25	27	33	32	39	8	9	13	4
T018	NA	NA	NA	36	39	NA	NA	NA	NA	NA
T019	34	16	24	31	31	55	11	13	13	1
T020	38	19	26	36	35	45	13	11	14	3
T022	37	22	25	26	24	61	13	15	15	0

Subject	WASI FSIQ	Digit Span forward	Digit Span backward
T002	107	6	5
T011	119	7	6
T012	109	6	4
T015	115	8	7
T018	107	7	6
T019	91	6	4
T020	100	7	6
T022	100	8	6

Abbreviations: CVLT-II, California Verbal Learning Test – second edition; del, delayed; FSIQ, Full Scale Intelligence Quotient; imm, immediate; LM, Logical Memory (Stories); reco, recognition; WASI, Wechsler Abbreviated Scale of Intelligence; WMS, Wechsler Memory Scale-III.

Table 5. Standard neuropsychological test results of healthy control participants

Subject	Memory									
	WMS LM imm (max 75)	WMS LM del (max 50)	WMS LM reco (/30)	WMS Faces imm (/48)	WMS Faces del (/48)	CVLT-II Learning Total (max 80)	CVLT-II Uncued imm (max 16)	CVLT-II Uncued del (max 16)	CVLT-II reco hits (/16)	CVLT-II false reco
C003	45	30	29	38	37	63	12	15	14	0
C005	47	31	28	38	43	NA	NA	NA	NA	NA
C009	53	31	28	40	40	NA	NA	NA	NA	NA
C011	54	31	26	32	30	62	14	15	16	0
C013	45	30	26	36	38	54	11	12	16	0
C014	57	41	29	46	46	71	16	16	16	0
C016	66	39	28	43	43	69	16	15	16	0
C017	39	21	25	35	32	55	12	11	15	4
C021	37	17	26	36	35	52	11	13	16	0
C022	58	35	29	NA	NA	73	16	16	16	0
C023	61	42	29	NA	NA	63	16	16	16	0
C024	38	24	23	29	29	45	10	11	14	3
C025	52	27	28	43	32	48	12	12	15	5
C026	49	33	26	42	34	62	13	15	16	0
C028	46	35	27	43	43	64	16	14	16	1
C029	64	44	29	42	41	74	15	16	16	0
C030	41	29	23	30	32	45	13	9	15	10
C031	65	47	30	45	46	67	15	16	16	1
C032	61	39	28	32	39	58	13	12	15	1
C034	50	31	27	39	38	76	14	16	16	1
C035	48	25	26	38	36	65	15	15	15	2
C036	54	34	29	43	37	66	14	14	15	0
C037	41	28	26	38	34	60	13	12	16	3
C038	39	25	27	35	36	57	8	7	16	10
C039	48	30	28	33	34	63	14	15	16	2
C040	48	27	26	34	33	55	13	10	13	1

Table 5. (cont'd)

Subject	WASI FSIQ	Digit Span forward	Digit Span backward
C003	114	7	5
C005	118	8	8
C009	115	9	8
C011	102	8	5
C013	113	7	4
C014	123	7	8
C016	118	8	6
C017	90	5	4
C021	115	8	5
C022	126	9	7
C023	113	7	7
C024	126	8	7
C025	118	8	5
C026	118	5	4
C028	105	5	5
C029	128	8	7
C030	119	7	5
C031	125	6	5
C032	128	7	6
C034	104	8	5
C035	104	5	5
C036	124	9	7
C037	94	7	4
C038	98	6	5
C039	90	7	4
C040	118	8	5

There was no difference between the three groups for full scale WASI IQ [$F(2,67) = 1.524$, $p = 0.225$]. On the memory measures, patients with temporal lesions performed generally lower than patients with frontal lesions and control participants. The performance of the patients with temporal lesions on the immediate [$F(2, 68) = 4.734$, $p = 0.012$] and delayed [$F(2, 68) = 6.198$, $p = 0.003$] recall of the Logical Memory subtest of the WMS-III was significantly lower than that of both patients with frontal lesions ($p = 0.017$; $p = 0.011$, respectively) and control participants ($p = 0.005$; $p = 0.001$, respectively), as shown by post-hoc Least Significant Difference (LSD) tests. A one-way ANOVA yielded a marginally significant group difference [$F(2, 57) = 2.537$, $p = 0.088$] on the immediate free recall of the first list of the CVLT-II. Post-hoc LSD test showed that patients with temporal lobe lesions recalled significantly fewer words than healthy subjects ($p = 0.028$). No other group comparisons of memory measures reached significance. Finally, on digit span forward [$F(2, 67) = 3.920$, $p = 0.025$], patients with frontal lesions performed significantly lower than patients with temporal lesions ($p = 0.023$) and healthy subjects ($p = 0.016$). On the digit span backward, a one-way ANOVA yielded a marginally significant group difference [$F(2, 66) = 2.483$, $p = 0.091$], suggesting that the patients with frontal lesions performed worse than patients with temporal lesions ($p = 0.040$). The mean scores and standard deviations for the three participant groups are presented in Table 6.

Table 6. Mean (SD) results on standard neuropsychological tests for the three groups

Tests	Participant groups		
	Frontal	Temporal	Healthy control
WMS LM imm (max 75)	48.73 (7.41)	42.63* (8.31)	49.92 (8.90)
WMS LM del (max 50)	29.58 (7.15)	23.95* (6.47)	31.38 (7.64)
WMS LM reco (/30)	27.21 (2.48)	25.82 (1.91)	26.96 (2.16)
WMS Faces imm (/48)	38.23 (5.32)	35.11 (5.60)	37.92 (4.82)
WMS Faces del (/48)	36.77 (4.37)	36.16 (5.36)	37.00 (4.84)
CVLT-II Learning Total (max 80)	58.79 (13.39)	55.88 (12.62)	61.13 (8.62)
CVLT-II Uncued imm (max 16)	12.58 (3.58)	11.29* (3.27)	13.42 (2.10)
CVLT-II Uncued del (max 16)	13.11 (3.57)	11.82 (3.19)	13.46 (2.54)
CVLT-II Reco Hits (/16)	15.26 (1.28)	14.59 (2.06)	15.21 (1.38)
CVLT-II False Reco	0.84 (2.06)	2.41 (3.48)	1.83 (2.88)
WASI FSIQ	109.12 (14.01)	107.00 (11.55)	113.31 (11.51)
Digit Span forward	6.44* (1.08)	7.21 (0.86)	7.19 (1.23)
Digit span backward	5.00* (1.25)	5.84 (1.34)	5.62 (1.33)

Abbreviations: CVLT-II, California Verbal Learning Test – second edition; del, delayed; FSIQ, Full Scale Intelligence Quotient; imm, immediate; LM, Logical Memory (Stories); reco, recognition; WASI, Wechsler Abbreviated Scale of Intelligence; WMS, Wechsler Memory Scale-III. * $p < 0.050$