Impairment only on the fluency subtest of the Frontal Assessment Battery after prefrontal lesions

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The Frontal Assessment Battery is a set of six subtests that is used widely 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.

Keywords: prefrontal cortex; frontal cortex; Frontal Assessment Battery; verbal fluency; dorsomedial prefrontal cortex

Abbreviations: FAB = Frontal Assessment Battery; SMA = supplementary motor area

Introduction

Many claims have been made about the functions of the prefrontal cortex (Stuss and 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 (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 in Nyhus and Barcelo, 2009), verbal fluency (Milner, 1964; Benton, 1968) and non-verbal fluency (Jones-Gotman and Milner, 1977) tasks, and the self-ordered pointing task (Petrides and Milner, 1982). In addition, various test batteries, such as the Executive Interview (EXIT-25; Royall, 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 et al., 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 et al. (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 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 and Takahashi, 2006). Corticobasal degeneration involves, bilaterally, the paracentral region, the supplementary motor area (SMA), the lateral prefrontal cortex, the basal ganglia and the thalamus (Lee et al., 2011). Note that the patients included in the study of Dubois et al. (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 (Withwell et al., 2009).

In conclusion, the FAB 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 FAB 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 >12 years ago, its wide clinical use, and its name implying assessment of frontal cortical function, the FAB 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 and Nakamura-Palacios, 2009). Among 148 recently reviewed studies that used the FAB, none 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 establish whether frontal cortical damage can yield impairments on the tasks that comprise the FAB.

Materials and methods

Participants

The participants were 45 patients of the Montreal Neurological Hospital who had undergone 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 of the SMA 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, 10 had lesions in the right frontal cortex and one patient had bilateral frontal cortical damage in the SMA. 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 [standard deviation (SD) 10.07] after their surgery or cerebrovascular accident, ranging from 5 months to 50 years.

The temporal group included 12 patients with left temporal lobe excisions 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 left temporal lobe 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 11 tumor resections, three were standard anterior temporal lobectomies, with the excision involving 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 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 4 months to 26 years and 2 months, with an average of 6.89 years (SD: 7.85). None of the patients had comorbid neurological or psychiatric disorders. Only patients with a full-scale Wechsler IQ score >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 \(F(43) = 0.344, P = 0.733\). The characteristics of each group are presented in Table 1.

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

### Procedure

The FAB was administered to the participants together with 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 1-min trial of the phonological version of verbal fluency: participants were asked to give as many words as they could, starting with a given letter of the alphabet (letter ‘s’). The third subtest examines the repetition of a 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 are asked 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 the 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 nine words, but more than two 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 ~10 min.

### 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.

A chi-square test of independence breaking down the FAB scores into eight 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 \(\chi^2 (28, n = 69) = 33.094, \text{ not significant (n.s.)}\). A level of \(P < 0.05\) was accepted as statistically significant. Because few participants obtained a total score of 14 or lower (Fig. 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.

| Table 1 Characteristics of participant groups |
|-----------------|----------------|----------------|----------------|----------------|----------------|
|                | Group          | Gender | Age            | Education      | Time since surgery | Wechsler IQ |
|                |                |        | (SD)           | (SD)           | (years)           | (SD)         |
|                | Male | Female | Mean           | Mean           | Mean              | Mean         |
| BF  0 | 1 | 54     | 19            | 11.92          | 121              |
| RF  2 | 8 | 55.2   | (9.93)        | 15             | 8.70             | 110.78       |
| LF  6 | 8 | 48.5   | (11.24)       | 15.43          | 3.55             | 109.36       |
| F   8  | 17 | 51.4   | (10.8)        | 15.4           | 5.94             | 110.38       |
| LT  8  | 4 | 44.42  | (11.7)        | 15.5           | 5.69             | 107.73       |
| RT  5  | 3 | 50.25  | (10.5)        | 13.88          | 8.68             | 106          |
| TC  13 | 7 | 46.75  | (11.34)       | 14.85          | 6.89             | 107          |
| TF  14 | 16 | 51.84  | (11.77)       | 15             | –                | 113.32       |

\(F = \text{frontal}; \text{LF} = \text{left frontal}; \text{RF} = \text{right frontal}; \text{BF} = \text{bilateral frontal}; \text{LT} = \text{temporal}; \text{RT} = \text{right temporal}; \text{HC} = \text{healthy control.}\)
in the FAB total score distribution between the five participant groups ($\chi^2 (16, n = 69) = 15.169, \text{n.s.}$).

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 [$P = 0.042$]. 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; $\chi^2 (4, n = 69) = 14.963, P < 0.01$]. Patients with left frontal lesions performed significantly worse on this subtest than patients with right frontal lesions [$\chi^2 (1, n = 24) = 8.571, P < 0.01$], patients with right temporal lesions [$\chi^2 (1, n = 22) = 4.197, P < 0.05$] and healthy controls [$\chi^2 (1, n = 39) = 9.032, P < 0.01$]. 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 [$\chi^2 (2, n = 69) = 4.919, n.s.$ for subtest 5; $\chi^2 (2, n = 64) = 6.145, P < 0.01$]. 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 (57.1%) were impaired on the verbal fluency subtest, that is, they had a score of ≤2, or generated nine 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 left frontal patients 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 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 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 was extensive damage to the anterior part of medial frontal lobe 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 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 SMA 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

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

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<th>LF</th>
<th>RF</th>
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LF = left frontal; RF = right frontal; LT = left temporal; RT = right temporal; HC = healthy control.

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.
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 reconstruction of the postoperative MRI 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 and Brett, 2000) to display them on the MNI brain. aalf = ascending anterior ramus of the lateral fissure; cc = corpus callosum; 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; icps = inferior post-central sulcus; iprs = inferior precentral sulcus; iprs-p = inferior precentral sulcus – posterior; iprs-s = inferior precentral sulcus – superior; If = 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.
Figure 5 The cortical lesions (in red) of the 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 reconstruction of the postoperative 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 and Brett, 2000) to display them on the MNI brain. Note that the anatomical data for patient F023 was 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.
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 lesion included the most rostral part of the insula, the entire pars orbitalis region (area 47/12) and, rostrally, the white matter 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 anterior most 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 10 cases with right frontal cortical excisions, even those that involved the entire prefrontal cortex (e.g. Patient F028, Fig. 6), were impaired on the verbal fluency task. Figure 7 shows the overlap of lesions for the right frontal patients. For two of the right frontal cases (Patients F015 and F022), we did not have access to the MRI of the lesions; the operation report of Patient F015 specified a corticectomy of the mid-SMA of the superior frontal gyrus extending 4 cm in the rostral-caudal axis and 2.5 cm in the dorsal-ventral axis.

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 et al., 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 versus 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.

**Discussion**

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 FAB 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 et al. (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 (Petrides and Milner, 1982; Thais and Petrides, 2008; Tsuchida et al., 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 and Petrides, 2003), 11 of the 22 frontal patients who were not impaired on the FAB exhibited an impairment (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 three categories completed
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 postoperative MRI for Patients F009, F011, F014 and on the standard MNI brain for Patients F004, F016, F019, F020 and F028. In the latter cases, tracings of the lesions were used with MRictr software (Rorden and Brett, 2000) to transfer 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.
and many perseverative errors). One patient with a perfect score on the FAB was able to complete six categories of the Wisconsin Card Sorting Test, but required 127 cards and he committed 27 perseverative errors. Another patient performed well on the Wisconsin Card Sorting Test (six categories in 87 cards), but had a lower score on the FAB (14/18). Although Wisconsin Card Sorting Test data were not available for all our patients, these results show that performance on the Wisconsin Card Sorting Test and the FAB are not necessarily related.

One subtest of the FAB 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 s. 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 after left frontal lobe damage (Milner, 1964; Benton, 1968; Perret, 1974; Stuss et al., 1998; Baldo et al., 2001; Henry and Crawford, 2004; Robinson et al., 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 (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 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-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 et al. (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.

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 and 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 and 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 and 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 PET study showing speech activation foci in the middle portion of the anterior cingulate region (Paus et al., 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 and Rajshekhar, 2000) and expressive speech (Rostomily et al., 1991; Ackermann et al., 1996; Zentner et al., 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 et al. (1996) reported long-lasting impairment in complex or high-speed speech tasks, such as verbal fluency.

Figure 8 Statistical map of the voxel-based lesion-symptom mapping analysis, shown on the 3D 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.
occurred in patients whose superior medial resection included at least 16% of the area activated during a preoperative functional MRI 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 et al., 1984), has been linked to damage of the left medial frontal cortex including, but extending beyond, the SMA (Rubens, 1975; Madseu et al., 1978; Racy et al., 1979; Alexander and Schmitt, 1980; Ross, 1980; Goldberg et al., 1981; Freedman et al., 1984; Ziegler et al., 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, have 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 and Wolfson, 1995), the number of total correct designs on a design fluency task (Possin et al., 2008), have been shown able to differentiate frontal from non-frontal 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 the phonological verbal fluency subtest (mental flexibility) was shown to be sensitive to injury of the frontal cortex, specifically the dorsomedial frontal cortical region in the left hemisphere. These findings underline 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.

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