doi:10.1093/brain/awu359 BRAIN 2015: 138; 456–471 | 456

BRAIN
A JOURNAL OF NEUROLOGY

Why do patients with neurodegenerative frontal syndrome fail to answer: 'In what way are an orange and a banana alike?'

Julien Lagarde,[1,2] Romain Valabrègue,[2,3,4,5] Jean-Christophe Corvol,[2,4,5,6,7] Béatrice Garcin,[2,5] Emmanuelle Volle,[2,5] Isabelle Le Ber,[2,4,5,6,8] Marie Vidailhet,[2,4,5,6] Bruno Dubois[2,4,5,6,8] and Richard Levy[2,4,5,9]

Concept formation is the ability to create an abstract link between dissimilar objects or thoughts and is crucial for abstract and creative thinking. This process is related to the integrity of the prefrontal cortex, given the altered performances reported in patients with frontal damage, particularly those suffering from the behavioural variant of frontotemporal dementia. However, the cognitive mechanisms and neural bases of verbal concept formation are not clearly understood. The present study was aimed at addressing the following unresolved issues regarding concept formation in the field of neurology and cognitive neuroscience: (i) Are alterations in concept formation specific to frontotemporal dementia or are they also present in other cortical neurodegenerative disorders such as Alzheimer's disease? (ii) Is impaired performance in concept formation due to cortical lesions specific to frontotemporal dementia or to a cortico-subcortical frontal syndrome? and (iii) What are the cognitive mechanisms and neural bases underlying concept formation? To address these questions, we designed the Verbal Concept Formation Task, an experimental paradigm based on the similarities test. Patients presenting with severe frontal dysfunction (frontotemporal dementia, $n = 18$, and the Richardson form of progressive supranuclear palsy, $n = 21$) or with medial temporal pathology (amnestic mild cognitive impairment or Alzheimer's disease, $n = 14$) and healthy participants ($n = 18$) were given the Verbal Concept Formation Task and a large battery of neuropsychological tests. In addition, all participants underwent 3D T_1-weighted MRI to analyse grey matter volume using voxel-based morphometry. Frontal patients were significantly impaired on the Verbal Concept Formation Task as compared to non-frontal participants ($P = 0.00001$). Global performance score was positively correlated with scores in cognitive tasks assessing executive functions and with grey matter volume in several areas, mostly in the frontal-basal-ganglion network. Two types of errors were observed in frontal patients. The most frequent was discriminating instead of grouping items ('linking deficit'). Patients also linked items on a concrete instead of an abstract basis ('abstraction deficit'). Linking and abstraction deficits were related to partially different areas: the linking deficit to the dorsal anterior cingulate cortex, right middle frontal gyrus and both inferior parietal lobules and the abstraction deficit to the head of the caudate nuclei and the left superior frontal gyrus. These data suggest that verbal concept formation requires the integrity of the prefrontal-basal-ganglion functional network. In addition, it can be divided into two distinct cognitive processes, which are underlain by two partially different neural networks.

1 Neurology of Memory and Language Unit, Department of Neurology, Centre Hospitalier Sainte-Anne, 75014, Paris, France
2 INSERM, UMR_S1127, ICM, F-75013, Paris, France
3 Centre de NeuroImagerie de Recherche (CENIR), Groupe Hospitalier Pitié-Salpêtrière, 75013, Paris, France
4 Sorbonne Universités, UPMC Univ Paris 06, UMR_S1127, ICM, F-75013, Paris, France
5 CNRS, UMR_7225, ICM, F-75005, 75013, Paris, France
6 AP-HP, Groupe Hospitalier Pitié-Salpêtrière, Department of Neurology, 75013, Paris, France
7 INSERM, Centre d'Investigation Clinique, CIC-1422, Groupe Hospitalier Pitié-Salpêtrière, 75013, Paris, France
8 National Reference Centre on Rare Dementias, AP-HP, Groupe Hospitalier Pitié-Salpêtrière, 75013, Paris, France
9 AP-HP, Hôpital Saint-Antoine, Department of Neurology, 75012, Paris, France

Received May 20, 2014. Revised October 6, 2014. Accepted October 18, 2014. Advance Access publication December 17, 2014

Correspondence to: Prof. Richard Levy,
AP-HP, Hôpital Saint-Antoine,
Department of Neurology,
184 rue du Fbg Saint-Antoine,
75571 Paris cedex 12,
France
E-mail: richard.levy@sat.aphp.fr

Keywords: frontotemporal dementia; executive functions; frontal lobe; basal ganglia; neuropsychiatry: imaging

Abbreviations: FTD = frontotemporal dementia; FAB = frontal assessment battery; MMSE = Mini-Mental State Examination; PSPr = Richardson form of progressive supranuclear palsy; VBM = voxel-based morphometry; WAIS = Wechsler adult intelligence scale

Introduction

Concept formation is the ability to make an abstract link between dissimilar objects or thoughts by extracting their meaningful common characteristics (Giovannetti *et al.*, 2001; Miller *et al.*, 2002, 2003; Green *et al.*, 2006; Hartman and Stratton-Salib, 2007). In humans, concept formation is an essential process for complex mental operations such as reasoning and creative thinking. It is assessed by several neuropsychological tests such as proverb interpretation, similarities tests [Frontal Assessment Battery (FAB) Dubois *et al.*, 2000; Wechsler Adult Intelligence Scale (WAIS) Wechsler, 1981]; the Wisconsin Card Sorting Test (Nelson, 1976) and the California Card Sorting Test or Delis-Kaplan Executive Function System (Lezak, 1995).

Patients suffering from the behavioural variant of frontotemporal dementia (FTD), a disease clinically characterized by the progressive alteration of personality (affective, emotional and vegetative control as well as motivation) and interpersonal interactions (social cognition) associated with cognitive dysexecutive syndrome (Piguet *et al.*, 2011), are particularly impaired in tasks assessing verbal concept formation. The mental processes and neural abnormalities behind the deficit in verbal concept formation (i.e. categorization based on abstract similarities between items) have not been analysed in-depth in patients with frontal lobe damage.

Several findings from neuropsychological and functional imaging studies have suggested that verbal concept formation depends on the integrity of the prefrontal cortex (Kramer and Quitania, 2007; Gläscher *et al.*, 2009). Performance on tasks assessing concept formation abilities has been associated with frontal cortical regions, especially the left frontal lobe, thought to be involved in abstract word processing (Binder *et al.*, 2005) and to provide abstract representations by selection and cognitive control mechanisms (Noppeney and Price, 2003). Concept formation deficits have been related to a defect in the putative top–down regulation of posterior regions (e.g. the left fusiform gyrus) by the prefrontal cortex (Goldberg *et al.*, 2007; Martin, 2007), leading to an altered ability to generate abstract 'verbally-mediated' representations, instead of 'image-based' ones (Noppeney and Price, 2004). Performance on the Wisconsin Card Sorting Test has been correlated with activation in the dorsolateral prefrontal cortex (Nagahama *et al.*, 1996). Performance on the Delis-Kaplan Executive Function System has also been correlated with left frontal lobe volume (Fine *et al.*, 2009), as has a total abstract-reasoning score based on similarities and proverb interpretation (Kramer and Quitania, 2007). The generation of inappropriate concrete responses in this latter task has been associated with lesions in the left lateral frontal lobe, whereas overall performance is significantly impaired in patients with lesions in the medial frontal cortex (Murphy *et al.*, 2013). A recent lesion-mapping study has shown that lower performance in verbal comprehension tasks of the WAIS, including the similarities subtest, is related to lesions in the left inferior frontal gyrus (Gläscher *et al.*, 2009), a frontal area that was also activated in a functional MRI study of taxonomic categorization (Sachs *et al.*, 2008).

Nevertheless, it is worth noting that other disorders in which direct cortical lesions are less pronounced, such as autism, have also been related to altered performance in tests of abstract thinking and concept formation with a bias towards concrete responses (Minshew *et al.*, 2002; Frith, 2003; Ropar and Peebles, 2007). Furthermore, as numerous cognitive components seem to contribute to verbal concept formation (Reverberi *et al.*, 2005; Fuster, 2008), it is likely that this process relies on a distributed network of brain areas, rather than a unique and circumscribed region. It is for this reason that we also assessed a group of patients presenting with the 'classic' Steele-Richardson form of progressive supranuclear palsy (PSPr), an atypical parkinsonian syndrome characterized by oculomotor palsy, gait disturbance and cognitive dysfunction (Williams and Lees, 2009). The subcortical lesions affecting cognitive and limbic prefrontal-basal-ganglion-prefrontal-cortex circuits in PSPr are severe, and have resulted in making the frontal-like impairments seen in PSPr the prototype of 'subcortical dementia' (Albert *et al.*, 1974), although the presence of direct cortical lesions predominantly involving the posterior portions of the frontal cortex is also well established (Verny *et al.*, 1996; Kertesz *et al.*, 2010). Furthermore, although PSPr and

behavioural variant FTD patients have distinct grey matter atrophy patterns when compared to controls, a direct comparison of these two groups did not reveal any difference that persisted after correction for multiple comparisons in a recent study (Lagarde *et al.*, 2013*b*). Based on their comparable clinical phenotype with regard to cognitive functions, characterized by a demonstrated severe dysexecutive syndrome in both cases, it would appear that behavioural variant FTD and PSPr patients can be pooled together into a 'frontal' group. Nevertheless, our aforementioned study also reveals that in spite of their mostly comparable clinical phenotypes and cortical atrophy patterns, the dysexecutive 'frontal-like' syndromes of behavioural variant FTD and PSPr are associated with partially divergent neural circuits (Lagarde *et al.*, 2013*b*). To summarize, the addition of patients with PSPr provides an opportunity to study the involvement of the frontal syndrome as a whole in poor concept formation abilities, regardless of the pathophysiological or topographic entity involved, and to look for possible quantitative or qualitative differences between patients with behavioural variant FTD and those with PSPr that could be instructive with respect to the neural bases of this cognitive process.

In clinical practice, patients with frontal damage usually provide two main types of inappropriate responses when performing a verbal concept formation task such as the similarities task, which relies on the ability to detect similarities between items and group them into abstract categories. When asked 'In what way are an orange and a banana alike?' these patients do not always spontaneously answer that they are both fruits, and many are not able to indicate that they belong to the same taxonomic category. These patients either remain stuck in concreteness, stating for instance that an orange and a banana share some perceptual features ('they are sweet', 'they have a peel', 'they can be eaten'...), or they emphasize the differences between them (e.g. 'an orange is round and a banana long') (Dubois *et al.*, 2000). The precise neurological substrate of these two types of inappropriate answers has never been directly addressed, and they have often been attributed to a general executive dysfunction (Giovannetti *et al.*, 2001). Could the unexpected answers (concrete link and discrimination) observed in frontal patients be explained by the disruption of a unique mechanism (e.g. a systematic bias towards concrete features or perceptual details instead of abstract and more global representations), leading to either the discrimination or the linking of items on a concrete basis depending on whether these perceptual features are either divergent or convergent, respectively? Contrarily, can this complex cognitive process be dissociated into distinct components, such as an ability to link items (i.e. to make and/or select a convergent representation) and an ability to provide an abstract (i.e. taxonomic) representation?

To study these issues, we designed a new experimental paradigm based on similarities, called the Verbal Concept Formation Task, for an optimized analysis of verbal concept formation. A test of similarities seemed to be the most appropriate methodology, as the answer consists of explicitly providing a link rather than choosing between alternatives. However, existing tests, such as the similarities subtest of the WAIS, are based on a small number of items, which are linked in some cases according to taxonomic category, but in other instances based on theme/mode (e.g. dictionary and directory: notion of alphabetical order) or general knowledge (e.g. rubber and paper: are obtained from trees). Our new experimental task was aimed at homogenizing the material, improving quantitative analysis and yielding stronger inferences by increasing the number of items. Concept formation performance was studied in healthy participants and compared to those of patients with behavioural variant FTD, Alzheimer's disease or amnestic mild cognitive impairment due to Alzheimer's disease, and PSPr. Finally, to investigate the cognitive mechanisms and neural bases underlying verbal concept formation, a dissection of the types of responses provided in the Verbal Concept Formation Task as well as their correlations to other neuropsychological tests were performed. We also correlated the scores obtained with grey matter volume for all participants, by performing an exploratory whole-brain analysis, without prespecified anatomical regions of interest, because of the lack of robust and converging information on this subject in the literature.

The aims of the present study are as follows: (i) to confirm the alteration of verbal concept formation in patients with behavioural variant FTD using abstract categorization, and to see if it is present to the same extent in Alzheimer's disease or amnestic mild cognitive impairment due to Alzheimer's disease, as has sometimes been stated; (ii) to verify if altered performance in concept formation depend on direct prefrontal lesions such as those present in behavioural variant FTD or if it could be explained by an indirect frontal syndrome (e.g. via dysfunctions of prefrontal-subcortical-prefrontal circuits); and (iii) to obtain new insights into the cognitive mechanisms and anatomical bases of verbal concept formation, and more precisely to verify the hypothesis that verbal concept formation relies on two distinct cognitive processes underlain by two, at least partially different, neural circuits.

Materials and methods

The ethics committee of the Salpêtrière Hospital (Paris, France) approved the study. All participants gave written informed consent.

Participants

Eighteen healthy middle-aged adults (aged 36 ± 10.2 years) were first enrolled in a preliminary experiment designed to shape and evaluate the relevance of our new task aimed at assessing verbal concept formation.

Seventy-one native French-speaking subjects were prospectively enrolled in the study: 18 subjects with probable behavioural variant FTD according to consensus criteria, i.e. a history of progressive and disabling development of at least

three of the six discriminating clinical features (behavioural disinhibition, apathy or inertia, loss of empathy, perseverative behaviour, hyperorality, executive deficit with relative sparing of memory and visuospatial functions), a significant functional decline and frontal and/or anterior temporal atrophy, hypoperfusion or hypometabolism on imaging performed prior to inclusion in the study (Rascovsky *et al.*, 2011); 21 subjects with PSPr according to consensus criteria, which included a gradually progressing disorder with an onset at or after the age of 40, vertical supranuclear gaze palsy and prominent postural instability within the first year of disease onset (Litvan *et al.*, 1996); 14 subjects with isolated or predominant hippocampal memory dysfunction, i.e. mild to moderate Alzheimer's disease or amnestic mild cognitive impairment due to Alzheimer's disease (Albert *et al.*, 2011; McKhann *et al.*, 2011) but without dysexecutive syndrome, assessed by the FAB (Dubois *et al.*, 2000) (i.e. a score $\geqslant$16); and 18 healthy controls. Patients were recruited in the Movement Disorders Unit and the Reference Centre for Rare Dementias of the Salpêtrière Hospital (Paris, France). All patients underwent a Mini-Mental State Examination (MMSE) and scored $\geqslant$20. These groups were matched for age and educational level as well as for disease duration in the patient groups. Healthy controls had neither a history of neurological/psychiatric disorders nor memory/cognitive deficits and none took psychotropic drugs. Patients showing a significant degree of semantic impairment that could interfere with the comprehension and execution of tasks, i.e. scores of $<$36/40 in the denomination task and $<$38/40 in the semantic pairing task of the Groupe de Réflexion sur les Evaluations COgnitives (GRECO) neuropsychological semantic battery (Batterie d'Evaluation des Connaissances Sémantiques-GRECO), according to normative data for individuals between 50 and 74 years (Merck *et al.*, 2011), were not included.

The Verbal Concept Formation Task

This task was modelled after the similarities subtest of the FAB (Dubois *et al.*, 2000) and aimed at assessing verbal concept formation (Supplementary material). It was composed of the 80 pairs of words (items) for which our healthy middle-aged subjects provided the highest proportion of correct answers ($>$95%), i.e. those with the least ambiguity, out of 90 initial pairs. The pairs of words were presented sequentially and subjects had to name their common conceptual link, i.e. the taxonomic category (Sachs *et al.*, 2008). Participants were asked for each item: 'in what way are … and … alike?' Items and instructions were presented both orally and visually on a computer screen. Subjects received no feedback on their answers and we only took into account the first answer, even if they were sometimes asked to clarify what they meant when necessary. The response time was measured manually and consisted of the time elapsed from the display of the items on the computer screen to the presentation of the complete answer.

Dissecting the qualitative pattern of performance in the Verbal Concept Formation Task

For 60 of 80 pairs of items, participants had to find and verbalize the abstract link between items, i.e. the taxonomic category. These 60 pairs were divided into three conditions, comprising 20 pairs of items each, to obtain more qualitative information, i.e. to verify whether and how the type of abnormal responses was conditioned by the characteristics of the pairs of words presented: (1) the two items had strong common perceptual features in addition to their conceptual similarity [e.g. 'an apple and an apricot': they are both fruits (abstract link), but they are also round, sweet, can be eaten…]; (2) the items belonged to the same taxonomic category but had strong divergent perceptual features, making it difficult to link them from a perceptual, concrete perspective (e.g. 'a puzzle and a spinning top'); (3) the items were abstract words that did not have obvious perceptual features (e.g. 'loyalty and courage'). These types of pairs of items were randomly administered, regardless of the condition they belonged to. Word characteristics (lexical frequency, imagery value, semantic distance) were adjusted in these three conditions, so that they could not influence the comparison of performances between them (Landauer *et al.*, 1998; Desrochers *et al.*, 2000; New *et al.*, 2004). We first considered the Global Performance Score, corresponding to the number of abstract links out of the 60 items for which this response was possible.

Second, in addition to the Global Performance Score, participants' answers were classified into three different categories: the expected abstract links, an inappropriate concrete link or discrimination. It was thus possible to compare the number of each type of inappropriate answer (concrete link or discrimination) and response times between conditions to study the influence of an item's characteristics on the subjects' performances. Third, we calculated two ratios to be able to consider the ability to abstract independently from the ability to link (i.e. without one being directly influenced by the other as is the case with the raw scores). The abstraction ratio represents the ability to provide abstract answers when able to link items. It was obtained by dividing the Global Performance Score by the total number of 'linking' responses, as follows:

$$\text{Abstraction ratio} = [\text{Global Performance Score}/(\text{abstract links} + \text{concrete links})] \times 100.$$

The linking ratio represents the ability to link the items when not able to provide abstract answers. It was obtained by dividing the number of concrete links by the total number of inappropriate answers, as follows:

$$\text{Linking ratio} = [\text{concrete links}/(\text{concrete links} + \text{discriminations})] \times 100.$$

We compared Global Performance Scores, scores obtained in the similarities subtest of the WAIS, abstraction ratios and linking ratios between frontal patients (behavioural variant FTD and PSPr) and non-frontal subjects (Alzheimer's disease and control subjects) using Mann-Whitney U-tests. Then, a Kruskal-Wallis analysis of variance followed by a Mann-Whitney test for pairwise comparisons was employed to compare data between the four groups of subjects. We also correlated these scores with demographic information and with the neuropsychological variables mentioned below in all subjects, using the Spearman rank correlation test. A Bonferroni correction was used for multiple comparisons. All statistical analyses were performed with Statistica 6 software (StatSoft).

It should be noted that in the remaining 20 of the original 80 pairs, the two items had no way of being linked together.

Instead, participants had to say that they differed and to specify in what way. These pairs were randomly distributed throughout the task session and participants were informed of the existence of these pairs prior to the start of the test. These items were important as they provided a situation in which discrimination became appropriate. Therefore, when discrimination responses were noted in the other 60 pairs, this could not be attributed to a simple misunderstanding of the task.

Standard neuropsychological evaluation

In addition to the Verbal Concept Formation Task, all subjects underwent a neuropsychological examination. Global intellectual efficiency was evaluated using the MMSE (Folstein *et al.*, 1975) and the Mattis Dementia Rating Scale (Mattis, 1988). Executive functions were assessed by the FAB (Dubois *et al.*, 2000), the similarities subtest of the WAIS (Wechsler, 1981), the modified Wisconsin Card Sorting Test (Nelson, 1976), letter and category fluencies and the Stroop Interference Test (Stroop, 1935). Environmental dependency syndrome was studied by separately considering grasping, imitation and utilization behaviours. Each behaviour was rated from '3' (absent) to '0' (present even when the subject was asked to stop), a score of '2' corresponded to hesitation (e.g. the subject asked what he was supposed to do), and a score of '1' corresponded to a spontaneous abnormal behaviour that could be stopped when the subject was asked to stop (Lagarde *et al.*, 2013*a*). The sum of these subscores provided an environmental dependency score ranging from zero to nine. Lastly, we studied perceptual processing using Navon hierarchical figures (e.g. an 'N' composed of small 'B's; Navon, 1977).

We compared demographic and neuropsychological variables between our groups using non-parametric Kruskall-Wallis tests. A Bonferroni correction was used for multiple comparisons.

Morphological examination

All images were acquired on a 3 T MRI scanner on the same day as the neuropsychological examination. Two patients with behavioural variant FTD and one with PSPr did not undergo MRI. High-resolution 3D MPRAGE T_1-weighted images were acquired using the following parameters: repetition time = 2.200 ms, echo time = 2.940 ms, slice thickness = 1 mm, and a field of view of 256 mm. We also performed T_2-FLAIR images to rule out any unnoticed lesions, especially ischaemic ones. The preprocessing procedure was the same as that used in previous studies and has been described elsewhere (Lagarde *et al.*, 2013*a*, *b*). To sum up, brain volumes were normalized to a template space, modulated by multiplying voxel values by non-linear components, which allows the absolute amount of tissue corrected for individual brain sizes to be considered without entering total intracranial volume as a covariate, and segmented into grey matter, white matter and cerebrospinal fluid using the VBM8 toolbox on SPM8 software (http://www.fil.ion.ucl.ac.uk/spm). Lastly, grey matter volume was smoothed with an 8 mm full-width at half-maximum Gaussian kernel to minimize individual gyral variations and we applied an explicit grey matter mask. SPM8 was used for all statistical analyses. We used voxel-based morphometry (VBM) to compare grey matter volumes in our groups of patients using a full factorial design, with age and sex as nuisance variables (Mechelli *et al.*, 2005; Friston *et al.*, 2007). We studied the following contrasts: controls > behavioural variant FTD; controls > PSPr; controls > Alzheimer's disease; and non-frontal subjects (i.e. controls and Alzheimer's disease) > frontal patients (i.e. behavioural variant FTD and PSPr). We reported a statistical threshold of $P < 0.05$ with a family-wise error (FWE) correction for multiple comparisons.

We also used VBM to correlate grey matter volume in our 68 subjects (two patients with behavioural variant FTD and one patient with PSPr did not undergo MRI) with the Global Performance Score, abstraction ratio and linking ratio, using a multiple regression design with age and MMSE score as nuisance variables. We used an exploratory (i.e. uncorrected) threshold of $P < 0.001$, taken at a minimal cluster size of 50 voxels.

Results

General and standard behavioural analysis

There was no significant difference between the groups based on age, gender, educational level, handedness, or disease duration, and between MMSE scores in the patient groups ($P > 0.05$) (Table 1).

As for the standard neuropsychological evaluation, the frontal score (FAB score) was pathological in behavioural variant FTD and PSPr patients, but not statistically different between these two groups of patients ($P = 0.38$). As defined by the inclusion criteria, the frontal score was normal in patients with Alzheimer's disease and control subjects and statistically different from that of behavioural variant FTD and PSPr patients ($P = 0.00001$) (Table 1). We found significant differences between: (i) patients and healthy controls for the Mattis Dementia Rating Scale total score ($P = 0.00001$); (ii) frontal patients (i.e. behavioural variant FTD and PSPr patients) and non-frontal participants for the Mattis Dementia Rating Scale initiation score, the number of errors in the Wisconsin Card Sorting Test, the score obtained in the WAIS similarities subtests, and letter and category fluency ($P < 0.003$); and (iii) patients with Alzheimer's disease and other participants for the Mattis Dementia Rating Scale memory score ($P = 0.00001$), as expected by the inclusion criteria (Table 1).

Note that, in the Navon hierarchical figures, six frontal patients failed to provide a global response (i.e. they were only able to identify the small letters and not the main letter).

Comparisons of grey matter volume between groups

Grey matter volume was decreased in behavioural variant FTD patients when compared to controls in areas of the right medial frontal gyrus, the left inferior frontal gyrus, the

Table 1 Comparison of the main demographic parameters and neuropsychological variables between our four groups of participants

	Behavioural variant FTD (n = 18)	PSPr (n = 21)	Alzheimer's disease (n = 14)	Controls (n = 18)	Comparison (Kruskall-Wallis test)
Age (years)	69.7 (9.7)	65.5 (6.5)	72.4 (9.3)	67.8 (5.2)	KW = 2.72, P = 0.436
Sex ratio (M/F)	10/8	8/13	4/10	7/11	–
Handedness (R/L)	16/2	19/2	13/1	16/2	–
Education (years)	12 (3.7)	11.7 (3.8)	13.7 (3.1)	11.6 (2.7)	KW = 4.32, P = 0.228
Disease duration (years)	5.4 (3.5)	4.4 (1.7)	5.1 (2.4)	–	KW = 0.18, P = 0.91
MMSE (score/30)	25.6 (3.3)	25.8 (2.7)	24.1 (2.6)	29.1 (0.7)	KW = 29.3, P = 0.00001*
FAB (score/18)	12.2 (3.2)	11.5 (2.1)	16.4 (0.7)	17.4 (0.6)	KW = 61, P = 0.00001*
DRS total (score/144)	126.3(10)	129.1 (9.9)	130.3 (4.5)	141.9 (2)	KW = 32.4, P = 0.00001*
DRS attention (score/37)	36 (0.93)	35.2 (2.05)	36.8 (0.4)	36.9 (0.3)	KW = 0, P = 1
DRS concept (score/39)	35.5 (3)	35.5 (2.4)	37.9 (1.2)	37.5 (1.4)	KW = 5.86, P = 0.12
DRS initiation (score/37)	28.2 (4.7)	30.4 (5.8)	33.8 (3.2)	36.8 (0.7)	KW = 26.7, P = 0.00001*
DRS memory (score/25)	20.7 (3.8)	22.6 (2.4)	15.8 (2.1)	24.6 (0.8)	KW = 29.8, P = 0.00001*
BECS (score/80)	77.3 (2.9)	78.6 (1.9)	78.5 (2)	79.4 (1.1)	KW = 7.5, P = 0.06
No. of errors WCST	16.9 (9.8)	13.6 (8.5)	6.2 (4.4)	4.4 (3.6)	KW = 18.13, P = 0.0004*
Letter fluency	10.9 (6.9)	11.8 (6.8)	21.5 (5.2)	20.1 (8.6)	KW = 23.8, P = 0.00001*
Category fluency	19.2 (8.1)	18.8 (9.8)	27.5 (10.5)	32.6 (8.7)	KW = 16.7, P = 0.0008*
T interference Stroop	45.6 (6.9)	52.7 (7.5)	50.6 (7)	48.7 (5.8)	KW = 5.1, P = 0.17
WAIS similarities score	11.9 (7.2)	15 (5.2)	19.3 (4.7)	21 (4.5)	KW = 10.2, P = 0.017

Mean (SD). Significant differences using a Bonferroni correction for 16 tests ($P < 0.003$) are indicated by an asterisk.
M = male; F = female; R = right-handed; L = left-handed; KW = Kruskall-Wallis test; DRS = Mattis dementia rating scale; BECS = Batterie d'évaluation des connaissances sémantiques; WCST = Wisconsin card sorting test.

left frontal rectal gyrus, the right uncus, the left anterior cingulate and the left superior temporal gyrus. Grey matter volume in patients with Alzheimer's disease was significantly decreased in the left and right parahippocampal gyri and in the right thalamus when compared to controls. Patients with PSPr, when compared to controls, presented with decreased grey matter volume in the right precentral gyrus, the left fusiform gyrus, the cerebellum, the right frontal rectal gyrus, the right parahippocampal gyrus, the right thalamus and the right inferior parietal lobule. A comparison between frontal patients and non-frontal participants showed decreased grey matter volume in the right medial frontal gyrus, the left rectal gyrus, the right anterior cingulate, the cerebellum, the right uncus, the right supramarginal gyrus, the left inferior frontal gyrus, the right superior temporal gyrus and the right precentral gyrus in the frontal group (Fig. 1 and Supplementary Table 1).

Question 1: Does Alzheimer's disease impair verbal concept formation to the same extent as behavioural variant FTD?

Performance in the Verbal Concept Formation Task

Statistical analysis revealed significant differences in the Global Performance Score between patients with behavioural variant FTD and non-frontal participants (P = 0.00007), and between patients with behavioural variant FTD and either group of controls: P = 0.002 for the comparison versus patients with Alzheimer's disease, and P = 0.004 versus healthy control subjects. These results were in line with those obtained for the similarities subtest of the WAIS, albeit more robust. There was no significant difference between patients with Alzheimer's disease and controls (P = 0.56) (Fig. 2A and B).

Morphological analysis

Global Performance Score was positively correlated with grey matter volume in the left and right angular gyri, the head of the left caudate nucleus, the right dorsal anterior cingulate, the left middle frontal gyrus, the right frontal lobe, and the right and left superior temporal gyri (Fig. 3A and Table 2).

Question 2: Can behavioural variant FTD-related cortical lesions adequately explain concept formation deficits?

Performance in the Verbal Concept Formation Task

Statistical analysis revealed significant differences in the Global Performance Score between frontal patients and non-frontal participants taken as a whole (P = 0.00001). Response times tended to be shorter in non-frontal participants than in frontal patients (P = 0.054). Global performance scores were also significantly different when considering either patients with behavioural variant FTD or PSPr alone on the one hand and non-frontal participants on the other: P = 0.0001 for patients with behavioural

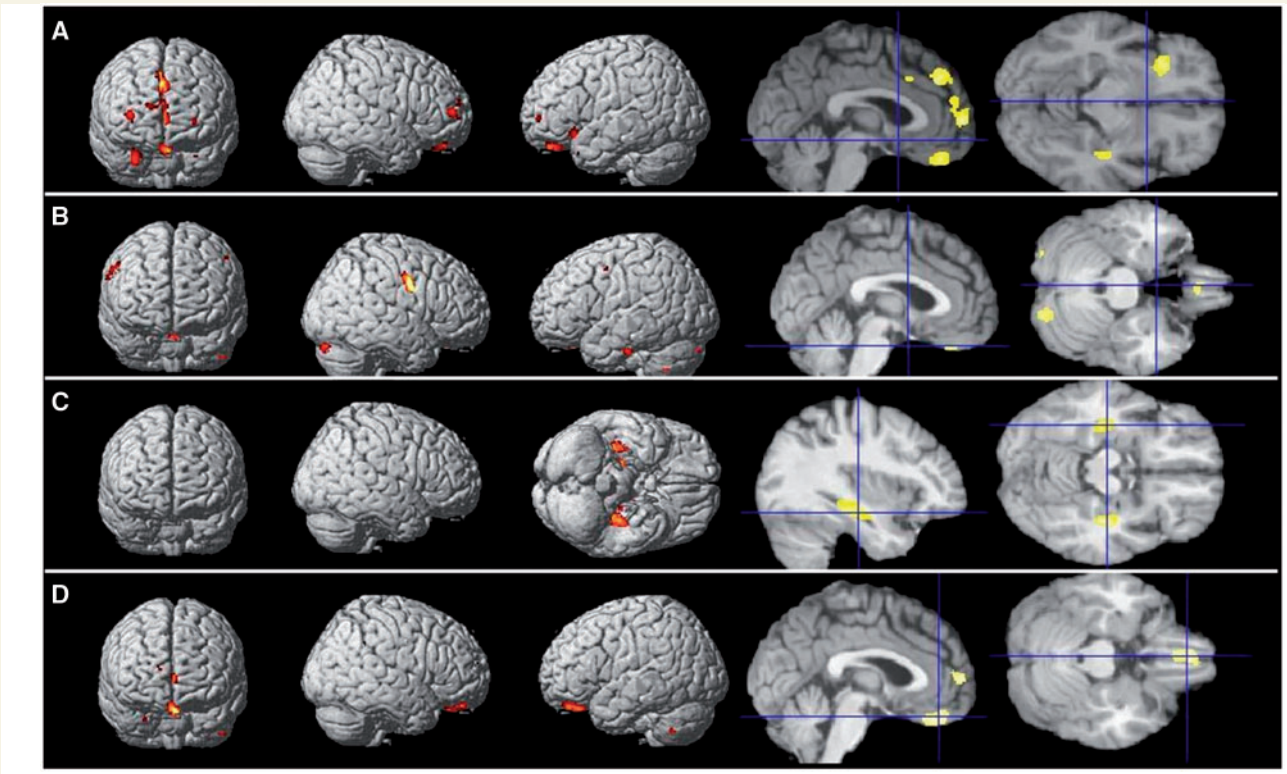

Figure 1 Results of the VBM analysis: comparison of grey matter volume between our groups of participants. (**A**) Zones of decreased grey matter volume in behavioural variant FTD patients when compared with controls ($P < 0.05$ with FWE correction for multiple comparisons). (**B**) Zones of decreased grey matter volume in patients with PSPr when compared with controls ($P < 0.05$ with FWE correction for multiple comparisons). (**C**) Zones of decreased grey matter volume in patients with Alzheimer's disease when compared with controls ($P < 0.05$ with FWE correction for multiple comparisons). (**D**) Zones of decreased grey matter volume in frontal patients compared with non-frontal participants ($P < 0.05$ with FWE correction for multiple comparisons).

variant FTD versus non-frontal participants, and $P = 0.007$ for patients with PSPr versus non-frontal participants. Nevertheless, scores in patients with PSPr were intermediate between patients with behavioural variant FTD and controls, and the difference between patients with PSPr and either of the two 'non frontal' groups did not persist after correction for multiple comparisons ($P = 0.04$ for PSPr versus Alzheimer's disease, and $P = 0.07$ for PSPr versus controls). The difference between the behavioural variant FTD and PSPr groups was not significant ($P = 0.15$) (Fig. 2A).

We performed correlations between the Global Performance Score and demographic or neuropsychological variables. We found significant correlations between the Global Performance Score and educational level, MMSE score, FAB score, WAIS score and the number of categories or errors in the Wisconsin Card Sorting Test ($P < 0.001$). No significant correlation was found with age (Table 3).

Morphological analysis

Adding patients with PSPr to the correlation analysis did not significantly modify the results reported for Question 1, as we found that the Global Performance Score was positively correlated with grey matter volume, albeit a little less robustly, in the same areas as reported above, namely the anterior cingulate, caudate nuclei, left, and to a lesser extent, right frontal lobes, and left angular gyrus (Fig. 3B and Table 2).

Question 3: What are the cognitive mechanisms and neural bases of verbal concept formation?

Performance in the Verbal Concept Formation Task

Comparisons of the abstraction ratio and linking ratio between groups showed significant differences between frontal patients taken as a whole and non-frontal participants in both instances: $P = 0.004$ for abstraction ratio and $P = 0.000003$ for linking ratio (Fig. 2C and D).

Nevertheless, when patient groups were considered separately, there was no statistically significant difference in the abstraction ratio (which reflects the ability to provide an abstract link between items) between groups ($P = 0.057$), whereas the linking ratio, which reflects the ability to find any link between items, was significantly decreased in behavioural variant FTD patients compared with either patients with Alzheimer's disease or controls ($P = 0.00002$

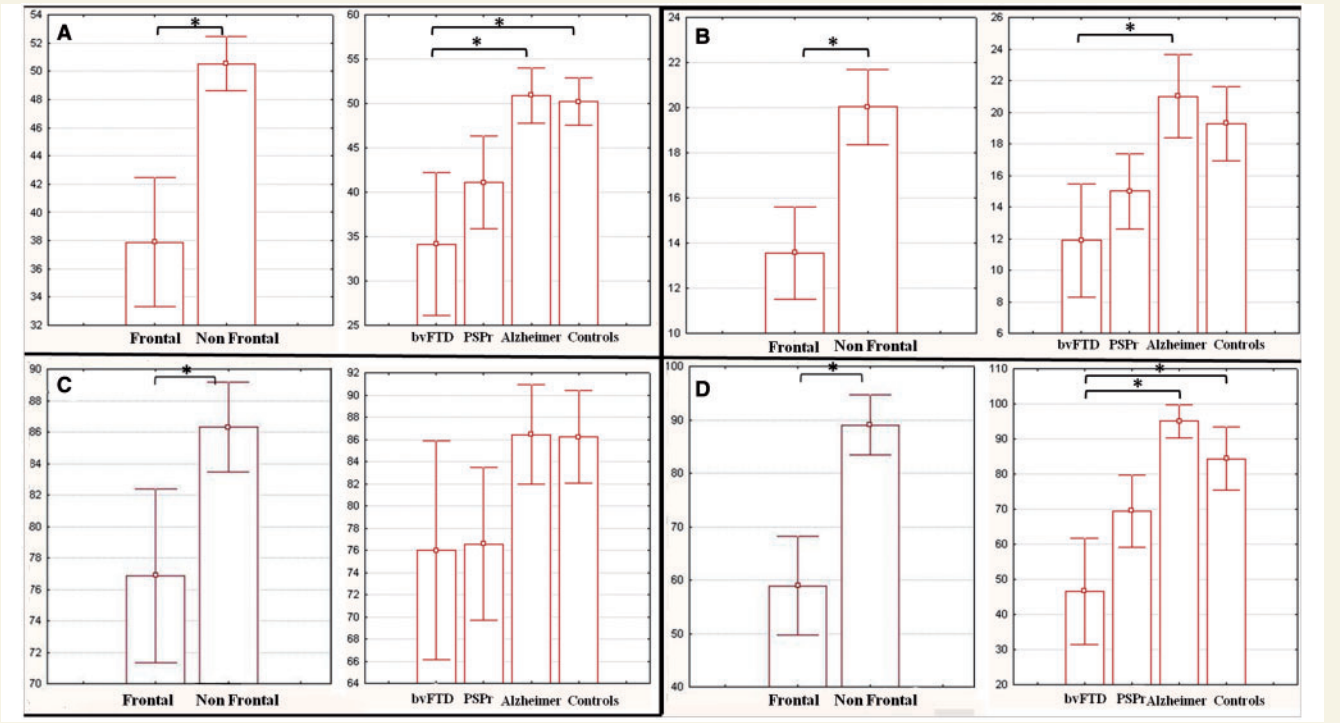

Figure 2 Results of the Verbal Concept Formation Task and the similarities subtest of the WAIS. Comparison of Global Performance Scores (**A**), scores obtained in the similarities subtest of the WAIS (**B**), abstraction ratios (**C**) and linking ratios (**D**). *Left* of each panel: Comparisons between frontal patients (behavioural variant FTD and PSPr) and non-frontal participants (Alzheimer's disease and controls). *Right* of each panel: Comparisons between the four groups of participants. Data are represented by means and 95% confidence intervals. Significant differences after a Bonferroni correction for six tests ($P < 0.008$) are indicated by asterisks.

and 0.002, respectively). No significant difference was found between behavioural variant FTD and PSPr patients ($P = 0.43$), even though the linking ratios tended to be lower in behavioural variant FTD patients (Fig. 2C and D).

Response times were shorter in condition 1 (in which similarities were related to both the taxonomic category and perceptual features of the items) than in the other two conditions for all participants, and especially for controls. Statistical significance was only reached when all the subjects were pooled together for a comparison between conditions 1 and 2 (in which items in a pair belonged to the same taxonomic category but had divergent perceptual features) ($P = 0.000003$) (Fig. 4A and B).

The number of discrimination responses was significantly higher in condition 2 than in condition 1 ($P = 0.00004$), and was also higher but to a lesser extent, in condition 2 than in condition 3 (where items were words defining abstract concepts and could only be linked according to their taxonomic category) for frontal patients who had a total number of discrimination responses $\geqslant 6$ (Fig. 4C). This latter value corresponded to the mean value calculated in healthy controls + two standard deviations (SD), and was therefore considered a threshold between normal and pathological scores.

We performed correlation tests between the abstraction ratio and linking ratio and demographic or neuropsychological variables in all subjects. We found significant correlations between our scores and educational level, the FAB score, the WAIS score, and the number of categories or errors in the Wisconsin Card Sorting Test ($P < 0.001$). It is also worth noting that both the abstraction ratio and linking ratio were correlated with the Global Performance Score, but they were not correlated with each other. No significant correlation was found with age, MMSE score, interference T-score in the Stroop test or the environmental dependency score (Table 3).

Morphological analysis

The abstraction ratio was positively correlated with grey matter volume in the head of the caudate nuclei bilaterally and in the left superior frontal gyrus. In contrast, the linking ratio was positively correlated with grey matter volume in the angular gyri bilaterally, the right dorsal anterior cingulate, and the right middle and left superior frontal gyri (Fig. 3C and D, Table 2). To eliminate the possibility that our results simply reflected the pattern of atrophy of the various patient groups rather than a genuine correlation with behavioural variables, we compared the two sets of anatomical zones to verify whether those that were correlated with our behavioural variables matched regions of maximum atrophy in patients with behavioural variant FTD, PSPr, and Alzheimer's disease as compared to controls, and in frontal patients versus non-frontal subjects, which was not the case (Fig. 1 and Supplementary Table

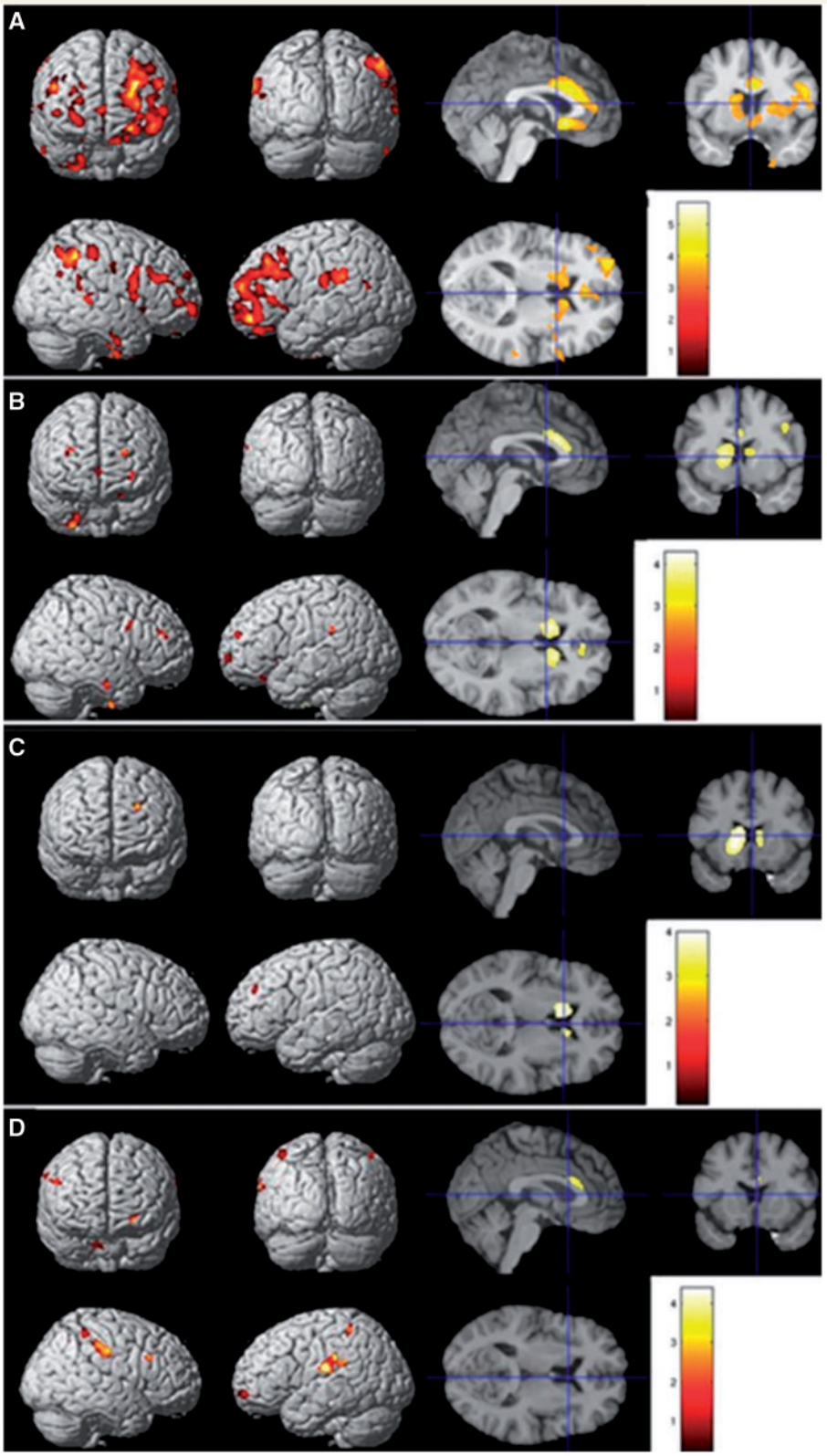

Figure 3 Results of the VBM analysis: correlations between grey matter volume and Global Performance Score, abstraction ratio and linking ratio. (**A**) Positive correlation between grey matter volume and Global Performance Score in behavioural variant FTD, Alzheimer's disease and controls (k = 50 voxels, $P < 0.001$). (**B**) Positive correlation between grey matter volume and Global Performance Score in behavioural variant FTD, PSPr, Alzheimer's disease and controls (k = 50 voxels, $P < 0.001$). (**C**) Positive correlation between grey matter volume and the abstraction ratio in all participants (k = 50 voxels, $P < 0.001$). (**D**) Positive correlation between grey matter volume and the linking ratio in all participants (k = 50 voxels, $P < 0.001$).

Table 2 Detailed results of the anatomical analysis

	Localization (Brodmann area)	MNI coordinates	Number of voxels	*Z*-score
Correlation with the Global Performance Score, in behavioural variant FTD, Alzheimer's disease and controls	Right angular gyrus	57 −51 51	1292	4.88*
	Left caudate nucleus	−18 21 −12	9936	4.77*
	Right anterior cingulate	2 20 21	9936	4.40
	Left angular gyrus	−68 −37 25	996	4.70*
	Left middle frontal gyrus	−26 33 43	5527	4.49*
	Right middle frontal gyrus	50 36 27	382	4.00
	Right superior frontal gyrus (10)	30 64 −2	540	3.93
	Right middle frontal gyrus	33 45 21	89	3.22
	Right superior temporal gyrus	69 −37 6	165	3.57
	Right inferior frontal gyrus	46 50 3	104	3.54
	Left middle frontal gyrus	−44 18 43	136	3.49
	Right middle frontal gyrus (9)	38 21 34	55	3.48
	Left superior temporal gyrus (22)	−58 −61 19	74	3.37
Correlation with the Global Performance Score in all participants	Right anterior cingulate	2 20 19	564	3.99
	Left caudate nucleus/putamen	−18 17 −2	1902	3.99*
	Right caudate nucleus	15 18 −2	1125	3.94*
	Left middle frontal gyrus	−24 51 21	59	3.6
	Right middle frontal gyrus	34 45 21	59	3.22
	Right inferior temporal gyrus	54 −14 −27	52	3.48
	Left inferior parietal lobule (40)	−70 −39 25	67	3.46
	Right anterior cingulate (32)	3 44 4	89	3.45
	Left superior frontal gyrus (10)	−32 65 1	59	3.32
	Right middle frontal gyrus	45 9 33	60	3.31
Correlation with the abstraction ratio in all participants	Left caudate nucleus (body)	−8 16 10	1483	3.6*
	Left superior frontal gyrus	−22 42 33	51	3.61
	Right caudate nucleus (head)	12 20 −6	395	3.44
	Anterior cingulate	9 42 4	54	3.27
Correlation with the linking ratio in all participants	Right inferior parietal lobule (40)	50 −30 45	435	4.09
	Left inferior parietal lobule	−58 −27 30	758	3.99
	Right inferior parietal lobule (40)	44 −42 56	80	3.74
	Right middle frontal gyrus	51 21 30	86	3.73
	Anterior cingulate	3 20 19	149	3.53
	Left superior frontal gyrus (10)	−26 62 −6	75	3.45

Areas in which grey matter volume is positively correlated with Global Performance Score in behavioural variant FTD, Alzheimer's disease and controls and in all participants and with the abstraction ratio and linking ratio in all participants (k = 50 voxels, $P < 0.001$ uncorrected). Clusters that are still significant at $P < 0.05$ after FWE correction for multiple comparisons at the cluster level are indicated by an asterisk. MNI = Montreal Neurological Institute.

1). We also derived normalized grey matter intensities for each subject for the 10 areas of interest found to be correlated with the abstraction and linking ratios, and correlated these 10 variables with each other. The finding that there were no strong and systematically significant correlations ruled out the possibility that our results merely reflected co-variation of atrophy in these zones in our group of subjects, independently of behavioural variables.

Discussion

The main results of this study can be summarized as follows: (i) patients with behavioural variant FTD were significantly impaired in our original Verbal Concept Formation Task as compared to healthy participants and patients with predominant memory impairment related to medial temporal lesions; (ii) a comparable, albeit slightly less pronounced impairment on the Verbal Concept Formation Task (when considering the Global Performance Score) was present in patients with PSPr. As demonstrated in a previous study (Lagarde *et al.*, 2013*b*), patients with PSPr share a severe 'prefrontal' dysexecutive syndrome with patients with behavioural variant FTD, which nevertheless relies on different neural circuits, with more widespread lesions affecting both cortical and subcortical structures, and accounting for comparable executive function alterations in spite of less pronounced direct

Table 3 Spearman rank correlation coefficients between Global Performance Score, abstraction ratio and linking ratio, and demographic and neuropsychological variables

	Global Performance Score	Abstraction ratio	Linking ratio
Age	0.09	0.16	0.03
Education	0.49*	0.39*	0.4*
MMSE	0.37*	0.31	0.24
FAB	0.69*	0.56*	0.55*
WAIS similarities subtest	0.88*	0.72*	0.67*
WCST no. of categories	0.65*	0.45*	0.59*
WCST no. of errors	−0.66*	−0.49*	−0.53*
T interference score Stroop	–	0.23	0.08
Environmental dependency score	–	0.38	0.16
Global Performance Score	–	0.87*	0.69*
Abstraction ratio	0.87*	–	0.35
Linking ratio	0.69*	0.35	–

Statistically significant values using a Bonferroni correction for 31 tests ($P < 0.001$) are indicated by an asterisk.
WCST = Wisconsin Card Sorting Test.

prefrontal damage. Indeed, as the basal ganglia are anatomically and functionally strongly associated with the prefrontal cortex (Alexander *et al.*, 1986), similar cognitive or behavioural impairments may result either from frontal lesions directly or from subcortical damage through a disconnection syndrome (D'Antona *et al.*, 1985). In addition, the Global Performance Score on the Verbal Concept Formation Task was correlated with performance in cognitive tasks assessing executive/frontal functions, such as the FAB, and with grey matter volume in several areas of the frontal-basal-ganglion network (i.e. the head of the caudate nuclei, the dorsal anterior cingulate cortex, and the left middle and superior frontal gyri). Correlations between grey matter volume and Global Performance Score were not significantly affected after the addition of patients with PSPr. This underlines the crucial role played by a prefrontal-basal-ganglion functional system in concept formation. Taken together, these results support and complete previous studies suggesting a link between frontal executive dysfunction and poor concept formation abilities (Maher *et al.*, 1985; Pillon *et al.*, 1986; Grafman *et al.*, 1990, 1995); (iii) two types of categorization errors were observed in frontal patients: the most pronounced was the inability to provide an answer linking the items of a given pair together (demonstrated by a significantly lower linking ratio), leading patients, especially in the behavioural variant FTD group, to provide answers based on divergent perceptual features. A less frequent but still significant type of error in frontal patients was the linking of items on a concrete basis (demonstrated by a significantly lower abstraction ratio) instead of an expected abstract link (i.e. the taxonomic category). The linking ratio and abstraction ratio were associated with partially different areas within the frontal-basal-ganglion system. Together, these data suggest that the difficulties faced by frontal patients in forming verbal concepts are associated with the dysfunction of two different cognitive processes, which are not disrupted to the same extent and which rely on two partially different neural networks: a predominant inability to link objects together, and impairment at the abstraction processing level.

The results obtained in the Verbal Concept Formation Task were in line with those obtained for the similarities subtest of the WAIS, albeit more robust. In effect, the differences reported in our study for the Global Performance Score in the Verbal Concept Formation task between frontal and non-frontal subjects were greater than those found in the same participants with another standard test assessing verbal concept formation, namely the similarities subtest of the WAIS (Fig. 2A and B). In sum, the Verbal Concept Formation Task seemed to be an efficient cognitive paradigm to detect and assess verbal concept formation impairment. Another important objective of the Verbal Concept Formation Task was to provide insight into the underlying mechanisms of verbal concept formation impairment in frontal patients. First, when designing the Verbal Concept Formation Task, we attempted to limit as much as possible the impact of non-specific factors that could prevent us from comprehending the essential components of this process: items and instructions were presented both orally and visually on a computer screen to focus the subject's attention and to limit the impact of working memory impairment, and we included subjects who performed normally on the French standardized 'Batterie d'Evaluation des Connaissances Sémantiques', which is a reliable tool for the detection of semantic and language impairment. Second, the Verbal Concept Formation Task was designed to qualitatively differentiate between categories of errors to provide clues as to the underlying cognitive/behavioural abnormalities responsible for global verbal concept formation impairment. As expected from clinical observations, frontal patients in our study provided two types of irrelevant responses: in some cases, they did not categorize at all and seemed to be stuck in the discrimination process, whereas in others, they linked the items but at the level of concrete characteristics instead of the expected abstract level. Nevertheless, the abstraction and linking ratios were not correlated with each other and were not disrupted to the same extent, as 'linking' ability was more compromised than its abstract counterpart, and more altered in behavioural variant FTD than in patients with PSPr, thus accounting for the trend towards lower Global Performance Scores observed in the former group (Fig. 2C and D). This difference could not be explained by the characteristics of the stimuli (divergent or convergent perceptual features), as the pairs with divergent perceptual features (which patients might have found more difficult to link) were not overrepresented in our task (20 of 60 pairs of items). Furthermore, there was an equal number of pairs of items (20 of 60) with common perceptual features (i.e. those that subjects could link on a concrete basis) as well

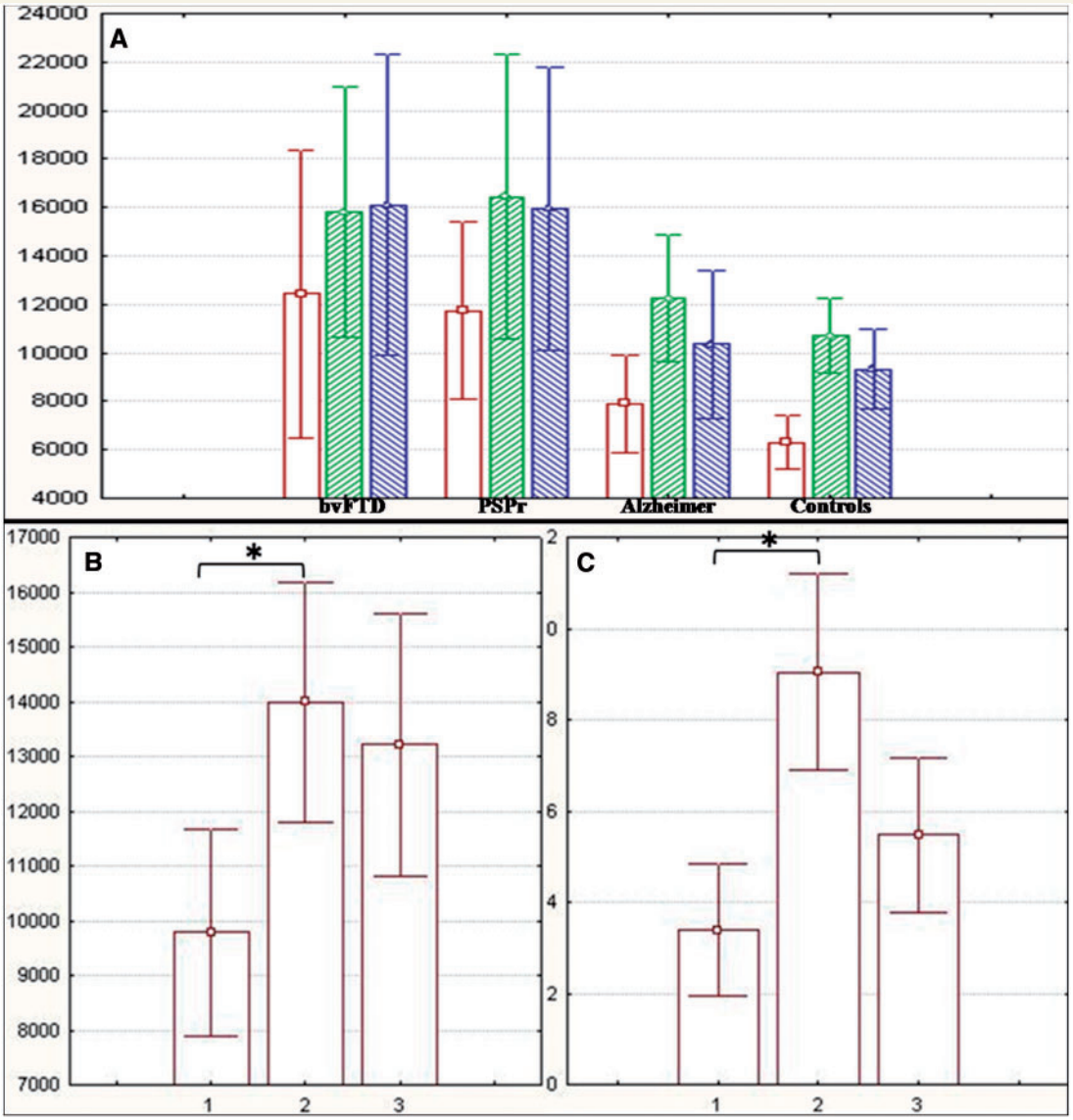

Figure 4 Detailed analysis of response times and types of abnormal responses in the Verbal Concept formation Task. Comparison of response times (in milliseconds) for conditions 1 (red), 2 (green) and 3 (blue) of the Verbal Concept Formation Task for each group of participants (**A**), comparison of response times (in milliseconds) for conditions 1, 2 and 3 for all participants taken as a single group (**B**), and comparison of the number of discrimination responses for conditions 1, 2 and 3 in frontal patients with the total number of discrimination responses $\geqslant 6$ (**C**). Significant differences are indicated by asterisks. bvFTD = behavioural variant FTD.

as pairs of items with no perceptual features (i.e. those that could not induce a bias towards concrete features). This indicates that the deficits observed were not due to the failure of a unique cognitive mechanism, as proposed in the 'weak central coherence theory', put forward to explain the detail-oriented cognitive style in autism spectrum disorders (Frith, 2003; Happé and Frith, 2006). Such a mechanism would lead to a bias towards concrete features or perceptual details, possibly favouring a similar tendency to either discriminate or link the items on a concrete basis according to their divergent or convergent perceptual features, and possibly to categorize abstract items more easily on an abstract basis. In our paradigm, this kind of mechanism would have resulted in equal numbers of the three types of responses (concrete links in condition 1, discriminations in condition 2 and abstract links in condition 3), thus leading to identical abstraction and linking ratios. Furthermore, no causal relationship could be inferred between the rareness of the abnormalities presented by frontal patients (only 6 of 39) in the Navon hierarchical figures test, aimed at detecting weak central coherence, and poor concept formation ability as measured by the Verbal Concept Formation Task.

Instead of a unique process, thus, our data strongly suggest that the verbal concept formation impairment may be related to the impairment of two partly independent

processes that are nevertheless often found together: (i) a 'linking' deficit (the inability to provide common links between items, which leads to the declaration of differences between items rather than common features); and (ii) an 'abstraction' deficit (the inability to find the abstract link between items, leading the patient to provide concrete similarities rather than the expected abstract answer). However, despite the fact that they are frequently concomitant, the first deficit seems to be more pronounced, especially in patients with behavioural variant FTD. We could thus infer that, in a normally functioning cognitive state, two groups of processes account for verbal concept formation under physiological conditions: first, the ability to link items, i.e. to implement a unique representation that is relevant to both items, and/or to suppress divergent perceptual representations, and second, the ability to access an abstract (categorical) representation, i.e. to be able to actively retrieve a taxonomic representation from one's (intact) semantic knowledge and/or to select the latter representation from other convergent features (Fig. 5).

How can one explain the 'linking deficit' in frontal patients? Two main hypotheses can be put forward: a deficit in the inhibition of divergent perceptual representations (i.e. the inability to prevent a discrimination process from running to its end, leading to the reporting of only discriminative features between items, even though these items have abstract or concrete common points), or a general deficit in implementing convergent representations. The first hypothesis (a deficit in inhibition) is supported by the significantly more pronounced difficulty to link items in condition 2 faced by the subgroup of frontal patients, who have the highest overall number of discrimination responses (Fig. 4C). Indeed, while this difference was noted for items in condition 2 of the Verbal Concept Formation Task, which exhibited more divergent perceptual features, it was not (or to a far lesser extent) for those in condition 3, which lack perceptual features (Fig. 4C). A deficit in implementing any convergent representation would have probably resulted in more homogeneous responses across all conditions of the Verbal Concept Formation Task, with a systematic inability to link the items of each pair, regardless of their perceptual characteristics. However, the linking ratio was not directly correlated with indices of cognitive (Stroop test) or behavioural (environmental dependency) inhibition. In addition, instead of the shorter reaction times, which could be due to impulsive responses, we observed longer response times in frontal patients when compared to controls. The latter phenomenon leads us to consider another hypothesis, namely that rather than reflecting a general slowing of mental processes in frontal patients, the prolonged response times observed in these patients in condition 2 could appear as a result of the slowing of a specific active process consisting of integrating representations from different sensory channels (e.g. visual, olfactory, tactile…). The extent of the slowing could be correlated to the degree of perceptual divergence of the items (Ramachandran and Hubbard, 2003), because the difference between response times in conditions 1 and 2 also exists in controls (Fig. 4A).

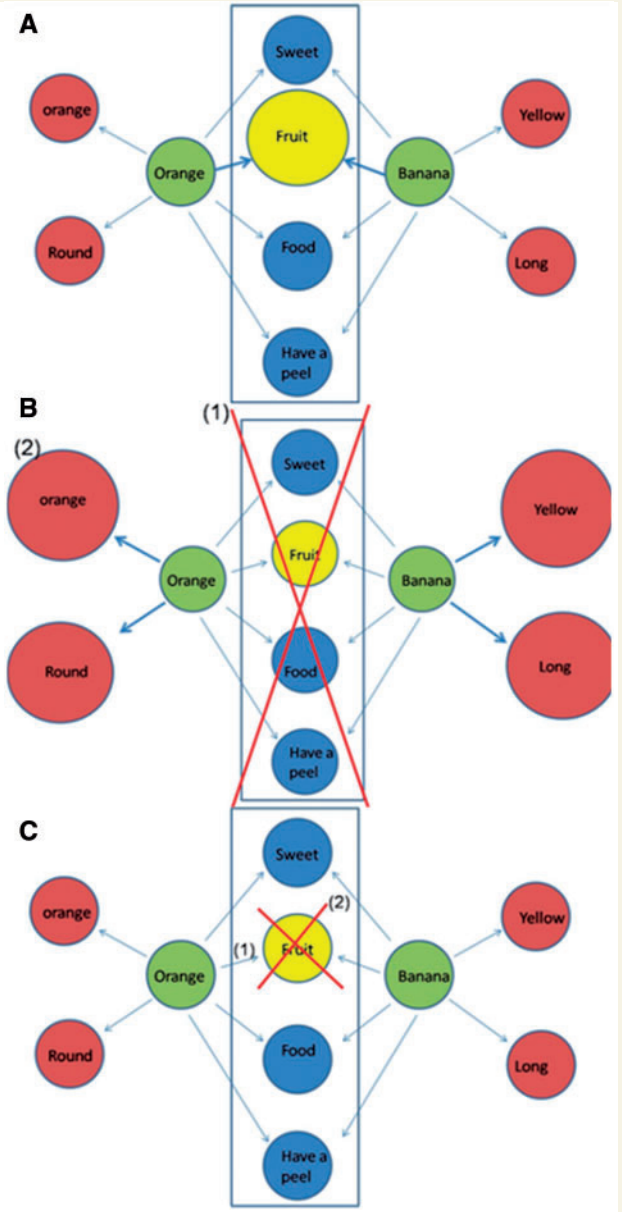

Figure 5 Putative cognitive mechanisms of verbal concept formation impairment. (**A**) In normal functioning, there is an advantage for abstract convergent representations over concrete convergent representations and divergent representations. (**B**) Failure to link items could result from an inability to implement any convergent representation (1) or from an abnormally high importance given to divergent representations, which are difficult to inhibit (2). (**C**) Failure to provide categorical representations even when able to link the items could result from a lack of the natural bias towards abstract representations, which are more difficult to select from other convergent representations (1), or from an inability to implement abstract representations (2).

Regarding the 'abstraction' deficit, if the ability to select an abstract representation among other convergent

representations were impaired, response times in condition 1, where pressure to select among representations shared by the items is higher as they have common perceptual features, would be longer than in condition 2 in frontal patients. However, we observed the exact opposite, not only in frontal patients, but also, as mentioned above, in controls. This result can also be explained by the mechanisms mentioned above, i.e. by the need to inhibit perceptual differences in condition 2, and/or to integrate representations from different sensory channels. Nevertheless, in frontal patients but not in controls, response times in condition 2 were not longer than in condition 3, where the absence of perceptual representation decreases selection demand without requiring the inhibition of divergent perceptual features or the integration of representations from different sensory channels. This is in favour of the participation of an active retrieval process for abstract semantic knowledge that is more prolonged in frontal patients than in controls when dealing with abstract items of the Verbal Concept Formation Task (see Fig. 4A).

At the level of symptom-lesion correlations, using the VBM technique, we also observed a relative dissociation between 'linking' and 'abstraction' mechanisms. Before considering the possible interpretations of these data, it is important to underline that the relatively limited number of participants, although similar or larger than in many other VBM studies, led us to use an 'exploratory' (i.e. uncorrected) threshold in whole-brain analysis. In addition, as mentioned in the introduction, we were not able to predefine regions of interest to increase statistical power because of the lack of sufficiently robust and converging evidence from prior studies.

The linking ratio was correlated with grey matter volume in the dorsal anterior cingulate and the angular gyri bilaterally. This result is in accordance with the 'inhibition' hypothesis, as the anterior cingulate has been linked to inhibitory control (Botvinick *et al.*, 2004; Kim *et al.*, 2011) and conflict monitoring, especially in its dorsal part (MacDonald *et al.*, 2000). The additional involvement of the angular gyri must be noted, as this region is known as a zone of convergence for representations from various sensory modalities and could be well suited to the task of creating new and sometimes unexpected links between objects, thus leading to abstract and creative thinking (Ramachandran and Hubbard, 2001), or at least to contribute to semantic retrieval and to supra-modal integration (Binder *et al.*, 2009).

The abstraction ratio was correlated with grey matter volume in the left superior frontal gyrus and the head of the caudate nuclei bilaterally (more markedly on the left side). With regard to the left superior frontal gyrus, this result is not surprising, as this prefrontal region has been repeatedly associated with abstraction processing (Burgess *et al.*, 2007; Garcin *et al.*, 2012). In contrast, the finding that the striatum is involved in abstraction processing may, at first sight, seem more surprising. To avoid any overstatement regarding the role of the striatum in abstraction, some caution is warranted when considering subcortical atrophy. Indeed, one cannot exclude the possibility that lateral ventricle dilatation accounts in part for this result, as VBM is not well suited to assessing subcortical atrophy. Nevertheless, we used a mask for grey matter, and more importantly, we considered MMSE scores, which are well correlated with lateral ventricle volume (Bigler *et al.*, 2004), especially in Alzheimer's disease, as a nuisance variable. Furthermore, this result was not systematically found in all our correlations, but only with the Global Performance Score and one of its components, the Abstraction Ratio, and was the only one that persisted after correction at the cluster level. In support of this finding, the striatum, especially the caudate nucleus, has been linked to a number of language or categorization processes (Mendez *et al.*, 1989; Grossman *et al.*, 2002; Crosson *et al.*, 2003; Gil Robles *et al.*, 2005; Teichmann *et al.*, 2008; Simard *et al.*, 2013; Chan *et al.*, 2013). Its exact role in this setting is still under debate and it has been suggested that it could relate to general executive language functions, such as facilitation of controlled as opposed to automatic processing (Copland *et al.*, 2000; Friederici, 2006) or the support of resource demands in categorization (Grossman *et al.*, 2002). More specific roles in language generation have also been claimed (Gil Robles *et al.*, 2005; Teichmann *et al.*, 2008), such as the participation of the left dorsal caudate in a loop encompassing the left pre-supplementary motor area and ventral anterior thalamus and underlying the retrieval of pre-existing lexical items versus competing alternatives (Crosson *et al.*, 2003), or the involvement of a frontostriatal loop in linguistic sequencing (Chan *et al.*, 2013). Activation in the caudate nucleus was recently found in a functional MRI study in association with a new lexical card-sorting task, and was restricted to semantic versus phonological decisions (Simard *et al.*, 2013). This result has been interpreted as being partly non-language-specific but instead related to category or rule retrieval amongst competing categories or rules stored in memory. Taken together, these other studies support our findings of a significant role of a prefrontal-striatal loop in abstract categorization, and more particularly, the involvement of the head of the caudate nuclei and left frontal lobe in access to abstract representations in verbal concept formation, either by actively facilitating the retrieval of a taxonomic category or by selecting among other convergent representations.

Conclusion

The results of this study first confirm the crucial role played by the 'prefrontal cortex/executive function anatomical-functional couple' in verbal concept formation. Second, our findings also expand our understanding of this process by providing novel clinical and anatomical insights: they show that this overall process hides two different subcomponents, namely 'linking' and 'abstraction' processes, which

account for different types of errors in patients with frontal damage. The two subcomponents are complementary: the 'linking' component allows us to integrate modality-specific representations by inhibiting the tendency to discriminate, while the 'abstraction' component helps us to actively retrieve and select abstract (i.e. taxonomic) representations. The fact that these two processes rely on different cortical and subcortical regions suggests that a dissociation in the nature of the deficit can be observed in patients depending on the exact location of the lesions, and that further analyses are necessary in patients with focal brain lesions in order to demonstrate double dissociations. In addition, the results of this study should encourage the validation of the Verbal Concept Formation Task in larger populations in order to provide a new tool to assess verbal categorization and concept formation in medical practice.

Funding

This work was supported by the Journées de Neurologie de Langue Française (JNLF) (for Julien Lagarde), and the Institut National de la Santé et de la Recherche Médicale (INSERM). The research leading to these results has received funding from the program 'Investissements d'Avenir' ANR-10-IAIHU-06.

Supplementary material

Supplementary material is available at *Brain* online.

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