doi:10.1093/brain/awr311 Brain 2012: 135; 201–215 | 201

BRAIN
A JOURNAL OF NEUROLOGY

Executive deficits are related to the inferior frontal junction in early dementia

Matthias L. Schroeter,[1,2,3] Barbara Vogt,[1] Stefan Frisch,[1,2] Georg Becker,[4] Henryk Barthel,[3,4] Karsten Mueller,[1] Arno Villringer[1,2,3] and Osama Sabri[3,4]

1 Max Planck Institute for Human Cognitive and Brain Sciences, 04103 Leipzig, Germany
2 Day Clinic of Cognitive Neurology, University of Leipzig, 04103 Leipzig, Germany
3 LIFE - Leipzig Research Centre for Civilization Diseases, University of Leipzig, 04103 Leipzig, Germany
4 Department of Nuclear Medicine, University of Leipzig, 04103 Leipzig, Germany

Correspondence to: Matthias L. Schroeter, MD, PhD, MA,
Max Planck Institute for Human Cognitive and Brain Sciences,
Stephanstr. 1A,
04103 Leipzig,
Germany
E-mail: schroet@cbs.mpg.de

Executive functions describe a wide variety of higher order cognitive processes that allow the flexible modification of thought and behaviour in response to changing cognitive or environmental contexts. Their impairment is common in neurodegenerative disorders. Executive deficits negatively affect everyday activities and hamper the ability to cope with other deficits, such as memory impairment in Alzheimer's disease or behavioural disorders in frontotemporal lobar degeneration. Our study aimed to characterize the neural correlates of executive functions by relating respective deficits to regional hypometabolism in early dementia. Executive functions were assessed with two classical tests, the Stroop and semantic fluency test and various subtests of the behavioural assessment of the dysexecutive syndrome test battery capturing essential aspects of executive abilities relevant to daily living. Impairments in executive functions were correlated with reductions in brain glucose utilization as measured by [^{18}F]fluorodeoxyglucose positron emission tomography and analysed voxelwise using statistical parametric mapping in 54 subjects with early dementia, mainly Alzheimer's disease and frontotemporal lobar degeneration, and its prodromal stages: subjective and mild cognitive impairment. Although the analysis revealed task-specific frontoparietal networks, it consistently showed that hypometabolism in one region in the left lateral prefrontal cortex—the inferior frontal junction area—was related to performance in the various neuropsychological tests. This brain region has recently been related to the three component processes of cognitive control—working memory, task switching and inhibitory control. Group comparisons additionally showed hypometabolism in this area in Alzheimer's disease and frontotemporal lobar degeneration. Our study underlines the importance of the inferior frontal junction area for cognitive control in general and for executive deficits in early dementia.

Keywords: Alzheimer's disease; executive functions; [^{18}F]fluorodeoxyglucose-PET; frontotemporal dementia; inferior frontal junction

Abbreviations: BADS = behavioural assessment of the dysexecutive syndrome; FTD = frontotemporal dementia; FTLD = frontotemporal lobar degeneration

Introduction

Executive functions describe a wide variety of higher order cognitive processes that allow the flexible modification of thought and behaviour in response to changing cognitive or environmental contexts (Stuss, 1992; Rabbitt, 1997). They are crucial for coping with the changing demands of everyday life. Executive

Received May 19, 2011. Revised August 22, 2011. Accepted September 18, 2011. Advance Access publication December 19, 2011

functions have been related to the frontal lobes, namely the anterior cingulate/posterior medial frontal cortex and lateral prefrontal cortices (Carter *et al*., 1998; Schroeter *et al*., 2002, 2007*a*; Derrfuss *et al*., 2004; Ridderinkhof *et al*., 2004). Work by Miyake *et al*. (2000) using a latent variable approach analysing data from a large sample of young adults on several complex cognitive tasks suggests that executive control may be best conceptualized as comprising at least three different component processes: working memory, task switching and inhibitory control. One comprehensive systematic and quantitative meta-analysis on studies with functional MRI using the activation likelihood estimate approach identified the inferior frontal junction area, a border zone between Brodmann Area (BA) 6/8/44, as essential for task switching and inhibitory control as measured by Stroop task performance (Brass *et al*., 2005; Derrfuss *et al*., 2005, 2009). Another wide-ranging activation likelihood estimate meta-analysis confirmed this finding and also demonstrated the relevance of this brain region for working memory in addition to a relevant overlap of the three cognitive component processes in the posterior medial frontal cortex (Christ *et al*., 2009).

A range of tests is used to measure executive functions. A 'classical' test is the Stroop colour-word interference task (MacLeod, 1991), where subjects are requested to name the colour of a word with an incongruent meaning. Subjects have to inhibit an overlearned response (reading) in favour of a novel response (colour naming). Interference resolution and response inhibition may be examined with this task. The verbal fluency task is another classical test involving executive functions. Here, subjects have to produce as many words as possible beginning with a specific letter or from a specific category (Crawford and Henry, 2005).

Since many patients with noticeably impaired adaptive behaviour in daily activities still score within the norms in neuropsychological testing, it has been discussed that classical executive tests do not capture essential aspects of executive abilities that are particularly relevant to daily living (Shallice and Burgess, 1991; Burgess, 1997; Rabbitt, 1997). These tests mostly have a specific goal, rules to be followed and are generally of a relatively clear structure—there may even be direct feedback concerning mistakes—all of which are generally uncommon for the demands of daily life. More recent test batteries such as the Behavioural Assessment of the Dysexecutive Syndrome (BADS; Wilson *et al*., 1996) incorporate these demands to a greater extent by tapping everyday executive functions. Indeed, the BADS is a better predictor of everyday problems than, for instance, the Wisconsin Card Sorting Test (Strauss *et al*., 2006).

Impairments in executive functions are frequent in neurodegenerative disorders. They negatively affect everyday activities and hamper the ability to cope with other deficits, such as memory impairment or behavioural disorders (Perry and Hodges, 1999). Frontotemporal lobar degeneration (FTLD), in particular its subtype frontotemporal dementia (FTD), is characterized by executive deficits besides serious changes in personality and behaviour (Neary *et al*., 1998, 2005; Perry and Hodges, 2000; Seeley *et al*., 2006; Schroeter *et al*., 2007*c*, 2008). Likewise, Alzheimer's disease is frequently associated with deficits in executive abilities, although in its prodromal stage, amnestic mild cognitive impairment, these are overshadowed by amnesia (Perry and Hodges, 1999; Baddley *et al*., 2001; Chen *et al*., 2001; Amieva *et al*., 2004; Bäckman *et al*., 2004, 2005; Blennow *et al*., 2006; Hodges, 2006; Tabert *et al*., 2006). Executive deficits might also predict conversion from mild cognitive impairment to Alzheimer's disease (Chen *et al*., 2001; Bäckman *et al*., 2004, 2005; Tabert *et al*., 2006) and the occurrence and progression of FTD (Geschwind *et al*., 2001; Hornberger *et al*., 2008).

So far, few imaging studies have related deficits in classical executive tests such as the Stroop interference or fluency task to atrophy and hypometabolism in prefrontal regions in FTLD, Alzheimer's disease and mild cognitive impairment (Salmon *et al*., 2006, 2008, 2009; Teipel *et al*., 2006; Bracco *et al*., 2007; Grossman *et al*., 2007; Huey *et al*., 2009; Pa *et al*., 2009; Raczka *et al*., 2010), although it is well known that these regions are altered in these diseases (Thompson *et al*., 2003; Apostolova *et al*., 2007; Schroeter *et al*., 2007*c*, 2008, 2009; Barthel *et al*., 2011).

Our current study aimed to systematically explore the neural correlates of executive functions by relating deficits in this domain to regional hypometabolism as measured with [^{18}F]fluorodeoxyglucose-PET in early dementia. Neuropsychological tests included in this study were chosen so as to cover different aspects of executive functions, namely inhibition of interfering information (Stroop Test), semantic or category fluency (Supermarket Test), problem solving (subtest Action Program from the BADS), planning (subtest Zoo Map Test) and strategy building (subtest Key Search from the BADS).

The cohort involved 54 subjects with various kinds of early dementia, mainly Alzheimer's disease and FTLD, and in the prodromal stages of subjective and mild cognitive impairment (Winblad *et al*., 2004; Jessen *et al*., 2010). Whereas subjective cognitive impairment is characterized by complaints of cognitive impairment that cannot be confirmed by neuropsychological testing, such impairments are detectable in mild cognitive impairment. We decided to involve such a broad group of subjects for several reasons: (i) we were interested in the neural correlates of executive functions *per se*, and this approach may increase variance and accordingly, statistical power; (ii) this method was applied successfully in recent comprehensive studies (Rosen *et al*., 2005; Rankin *et al*., 2006); (iii) Alzheimer's disease and FTLD have recently been discussed as occurring in a spectrum of neurodegenerative brain diseases (van der Zee *et al*., 2008); and (iv) previous studies indicated that executive deficits have similar severity, and are related to regionally similar neural correlates in different kinds of dementia, such as Alzheimer's disease and FTLD (Hutchinson and Mathis, 2007). Although the latter view has been questioned, at least for fluency and regional atrophy in FTLD subtypes (Laisney *et al*., 2009; Libon *et al*., 2009), our approach may prevent the possibility that we just replicate disease-specific regional structural or functional alterations in the correlation analyses, because we correlate deficits across a spectrum of neurodegenerative diseases.

We hypothesized that executive deficits in early dementia and its pre-stages are mainly associated with hypometabolism in prefrontal regions (Carter *et al*., 1998; Schroeter *et al*., 2002, 2007*a*; Ridderinkhof *et al*., 2004; Derrfuss *et al*., 2005, 2009). Because it is well known that behavioural disorders are also influenced by impairments in frontal lobe function (Rosen *et al*., 2005;

Schroeter *et al*., 2007*c*, 2008, 2011; Raczka *et al*., 2010), we compared our results with the neural correlates of behavioural disorders as measured with the Neuropsychiatric Inventory in the same cohort as published in a previous paper (Schroeter *et al*., 2011). Finally, we identified brain regions affected in dementia by comparing regional metabolism in Alzheimer's disease and FTLD with subjective cognitive impairment as a control group. We chose this control group, because subjects with subjective cognitive impairment are not impaired in neuropsychological testing, and accordingly show a normal age-related decrease in cognitive performance. This control group is particularly suitable for diagnostic reasons, because in clinical practice it is crucial to discriminate between these subjective cognitive impairment subjects and patients with an early stage of dementia (Dukart *et al*., 2011). The subjective cognitive impairment cohort offers the unique opportunity to regard it both as a pre-stage of dementia and a control group—an advantage that is underlined by the ethical problems of conducting [^{18}F]fluorodeoxyglucose-PET in healthy subjects due to radiation exposure.

Materials and methods

Subjects

Fifty-four subjects who were admitted to the Day Clinic of Cognitive Neurology at the University of Leipzig were included in this study. They had presented with complaints of cognitive and/or behavioural alterations by their own account or by the account of caregivers. Investigations included a high-quality [^{18}F]fluorodeoxyglucose-PET scan, a comprehensive neurological and psychiatric history and examination, neuropsychological rating of behavioural deficits (Neuropsychiatric Inventory), testing of memory, executive function, attention and language (Schroeter *et al*., 2005, 2007*a*, *b*, 2010), structural MRI or CT scans, and lumbar puncture. Symptom severity was measured with the Clinical Dementia Rating Scale (Morris, 1997). Although this instrument has been developed for Alzheimer's disease, to date no instrument is available that considers all the different dementia syndromes equally. Patients were excluded if structural imaging revealed lesions due to stroke, traumatic head injury, brain tumour or inflammatory diseases. All data were acquired for diagnostic purposes. Informed consent was obtained from subjects to analyse these data retrospectively. The research protocol was approved by the ethics committee of the University of Leipzig, and was in accordance with the latest version of the Declaration of Helsinki.

Groups consisted of patients with probable Alzheimer's disease ($n = 19$; McKhann *et al*., 1984; Dubois *et al*., 2007), FTLD ($n = 13$; FTD = 3, semantic dementia = 6, mixed type = 4; Neary *et al*., 1998) and 'other dementias' ($n = 10$; posterior cortical atrophy $n = 3$, dementia with Lewy bodies $n = 2$, corticobasal degeneration $n = 1$, logopenic aphasia $n = 1$, dementia with symptoms of Alzheimer's disease/FTD $n = 2$ and with symptoms of Lewy body dementia/posterior cortical atrophy $n = 1$; McKeith *et al*., 1996; Mendez *et al*., 2002; Boeve *et al*., 2003; Gorno-Tempini *et al*., 2004). Two other patients suffered from mild cognitive impairment, presenting with complaints of cognitive impairment and were at least 1.5 SD below average performance in neuropsychological testing (Winblad *et al*., 2004). Another group presented with complaints of cognitive impairment that could not be confirmed by neuropsychological testing (subjective cognitive impairment; $n = 10$).

Group differences of clinical characteristics (Table 1) were examined with one-way ANOVAs followed by unpaired two-tailed *post hoc* Student's *t*-tests (Bonferroni corrected and adjusted for inequality of variance if necessary). As expected, Clinical Dementia Rating Scale as a measure of symptom severity differed between groups. Mean Clinical Dementia Rating Scale was ~1 in all three dementia groups, indicating early stages of disease. *Post hoc* Student's *t*-tests revealed higher values in dementia than subjective cognitive impairment (Alzheimer's disease/FTLD/other dementias versus subjective cognitive impairment $T = -3.9, -3.6, -4.3$; df = 27, 21, 18; $P < 0.05$). Mean age differed significantly between groups, in particular, between subjective cognitive impairment and Alzheimer's disease/other dementias ($T = -3.4, -3.6$; d = 27, 18; $P = 0.02$), whereas there were no differences regarding education, duration of symptoms and sex between groups.

Table 1 Characteristics of subjects and test results

	Subjective cognitive impairment	Mild cognitive impairment	Alzheimer's disease	FTLD	Other dementia	Group difference
n	10	2	19	13	10	
Age (years)	55.1 ± 5.0	62.5 ± 4.9	62.6 ± 6.0	61.1 ± 6.6	64.9 ± 7.2	3.6, **0.01**[a]
Sex (female/male)	4/6	1/1	12/7	7/6	4/6	2.1, 0.71[b]
Education (years)	12.4 ± 3.2	13.0 ± 4.2	10.1 ± 2.6	11.2 ± 3.7	12.1 ± 3.1	1.3, 0.29[a]
Duration (months)	42.2 ± 21.9	32.0 ± 14.1	39.7 ± 34.1	40.2 ± 17.4	45.2 ± 50.9	0.1, 0.98[a]
Dementia severity (Clinical Dementia Rating Scale)	0.25 ± 0.26	0.50 ± 0.0	0.87 ± 0.47	0.81 ± 0.43	0.95 ± 0.44	4.8, **0.002**[a]
Stroop task (s)	1.3 ± 0.3	1.4 ± 0.3	4.2 ± 2.4	4.6 ± 2.9	3.3 ± 1.9	3.4, **0.02**[a]
Category Fluency (words per min)	23.0 ± 2.2	12.0	12.0 ± 5.2	10.1 ± 7.8	9.1 ± 5.3	4.4, **0.006**[a]
Action Program (0–5)	5.0 ± 0.0	4.5 ± 0.7	3.5 ± 1.8	3.4 ± 1.4	3.4 ± 2.1	1.1, 0.36[a]
Zoo Part 1 (0–8)	6.7 ± 2.5	2.0 ± 2.8	0.53 ± 1.1	5.0 ± 3.7	0.0 ± 0.0	14.8, **<0.001**[a]
Zoo Part 2 (0–8)	8.0 ± 0.0	7.0 ± 1.4	5.4 ± 3.0	7.6 ± 1.3	2.5 ± 2.1	6.0, **0.001**[a]
Key Search (0–16)	14.3 ± 2.4	11.5 ± 5.0	10.4 ± 4.2	6.7 ± 3.9	9.4 ± 5.2	4.4, **0.005**[a]

a As tested with one-way ANOVA: *F*, *P*.
b As tested with two-tailed test: χ^2, *P*. Four degrees of freedom for each test. Mean ± standard deviation.
Significant values ($P < 0.05$) are written in bold.

Measurement of executive functions and behavioural impairment

In the Stroop Test, subjects are shown a list of names of colours (e.g. 'red', 'blue', etc.). In the critical incongruent condition, the print colour never corresponds to the colour of the written word. The subjects are asked to name the colour the word is written in. Here, they have to inhibit the overlearned response, reading the word (MacLeod, 1991; Schroeter *et al*., 2002, 2003, 2004, 2007*a*, *b*; Derrfuss *et al*., 2005). Response times for the critical condition per word were included in the analysis (Oswald and Fleischmann, 1986; Wolfram *et al*., 1986). The Supermarket Test is a test of semantic or category fluency that has recently been shown to be a very sensitive marker of cognitive decline in dementia (Cerhan *et al*., 2002). Subjects are asked to name as many different things that are available in a supermarket within a given time limit. This test is contained in the DemTect, a German language screening test for early dementia (Kalbe *et al*., 2004). The number of correct words given in 1 min was included in the analysis.

The BADS (Wilson *et al*., 1996) is a battery consisting of six different subtests that are all intended to tap everyday executive functions. In each subtest, performance is indicated in raw scores, which are then transformed into profile scores. Since profile scores are much less fine-grained compared with raw scores, we used the latter in all subtests for the correlation analysis. The Action Program task is conceptualized to test practical problem-solving abilities. Patients are instructed to extract a small cork from a tube using a set of different materials in a five step procedure. Scoring is based on how much help the patient requires from the examiner; raw scores range from 0 (no solution) to 5 (perfect solution without help). The Zoo Map Test taps into abilities of planning. In this test, a route has to be found in order to visit six designated locations on a map of a zoo, following certain rules. It consists of two parts: the Zoo Map Test 1 is highly demanding since little external structure for solving the task is provided; the Zoo Map Test 2 demands are much lower, since patients are simply asked to follow a pre-specified order of steps. Each part is scored according to certain criteria (number of locations visited, breaking rules, etc.) ranging from 0 to 8. In the Key Search subtest, subjects need to generate a strategy to search a field for a lost key, marking their path on a sheet using a pen. The efficiency of their strategy is scored by means of a set of criteria from which a total raw score ranging from 0 to 16 is computed.

Behavioural impairment was assessed with the Neuropsychiatric Inventory, a validated, caregiver-based behavioural rating system (Cummings, 1997). This inventory evaluates 12 major behavioural disorders in dementia, which include delusions, hallucinations, depression, anxiety, aggression/agitation, euphoria, apathy, irritability/lability, disinhibition, aberrant motor behaviour, sleep disturbances, and changes in appetite and eating behaviour. A composite score is calculated for each domain by multiplying the values for frequency (1–4/occasionally to very frequently) and severity (1–3/mild–severe).

For some subjects, test results for all tests were not available as, for practical reasons, tests were adapted to clinical needs. Some tests could not be carried out due to lack of time and/or reduced patients' capability. For instance, the Zoo Map Test cannot be performed in subjects with remarkable impairments in the understanding of instructions. Potential relationships between executive deficits and behavioural impairments were examined with Pearson's correlation coefficients.

[^{18}F]fluorodeoxyglucose-PET imaging and analysis

Dynamic PET scans were acquired after intravenous injection of 370 MBq [^{18}F]fluorodeoxyglucose using an ECAT EXACT HR + scanner (CTI/Siemens) in 2D mode simultaneously collecting 63 slices with an axial resolution of 5 mm full width at half maximum and an in-plane resolution of 4.6 mm. Subjects fasted for one night before PET imaging. Basic image processing and voxel-based data analysis were performed using Statistical Parametric Mapping (SPM5) routines (Wellcome Department of Cognitive Neurology; http://www.fil.ion.ucl.ac.uk/spm) implemented in Matlab 6.0 (Mathworks Inc.).

The 30–60 min post-injection time frames of the dynamic PET scans were realigned and a mean image was created for each subject. To enable an interindividual comparison of the subjects' regional brain [^{18}F]fluorodeoxyglucose uptake, each voxel of the mean images was normalized to the average intensity value of the cerebellum, which is one of the least affected regions in dementia (Yakushev *et al*., 2008; Dukart *et al*., 2010, 2011). After this activity normalization, PET image data were non-linearly spatially normalized into Montreal Neurological Institute (MNI) space using the SPM5 standard PET brain template. Normalized images were represented with $2 \times 2 \times 2$ mm voxel size. As a final preprocessing step, images were smoothed with a Gaussian kernel of 12 mm full width at half maximum.

Correlation between glucose utilization and executive functions

[^{18}F]fluorodeoxyglucose-PET images and the scores of the various executive tests of each of the 54 subjects were entered into a design matrix and the relationship between changes in glucose utilization and executive deficits was analysed using the general linear model. The significance of each effect of interest was determined using the theory of Gaussian fields. More precisely, test scores of each test/subtest were entered into separate 'multiple regression' design matrices. Age was always included as an additional covariate, as patterns of glucose utilization have been shown to change with increasing age and age differed between groups (Loessner *et al*., 1995; Dukart *et al*., 2010).

The relationship between voxel values of glucose utilization and the executive impairment of interest was examined with a-1 *t*-contrast, with the assumption that increasing severity of executive deficits would be associated with decreased glucose utilization. Diagnosis was generally not included in the model so as to provide greater variability of the data, since we were interested in the neural correlates of executive deficits across the various dementia subtypes, and different subtypes overlap with regard to these impairments. For display purposes illustrating the relevant clusters, we used $P < 0.001$, uncorrected for multiple comparisons. We identified brain regions that remained significant after correction for multiple comparisons on the cluster level with a statistical threshold of $P < 0.05$. Data were analysed at the whole brain level to avoid any *a priori* assumptions.

Conjunction analysis across various executive deficits

As discussed above, several aspects of executive functions have been suggested to be associated with frontal lobe function. To identify the most important and consistent brain regions involved in executive deficits, we conducted a conjunction analysis across the neural

correlates of the various executive tasks (for this analysis, results of the correlation analysis with $P < 0.001$, uncorrected for multiple comparisons, were used). The first conjunction analysis investigated the overlapping brain regions. The respective *t*-maps were transformed into maps of *z*-scores. Then, for each voxel, we computed the number of *z*-maps (executive functions) whose value in this voxel was above the threshold 3.1 ($P < 0.001$). In a second analysis, we generated a map which shows the minimum *z*-value for all executive functions for each voxel. This map corresponds to a conjunction analysis in the sense of a logical 'AND' of all input images (Nichols *et al*., 2004).

Dissociation between executive and behavioural deficits, and group comparisons

To investigate the relationship between executive and behavioural impairments, we compared the results of the present conjunction analysis to our previous data from a similar study on behavioural deficits, which systematically investigated their neural correlates in exactly the same cohort (Schroeter *et al*., 2011). The comparison was again performed using a conjunction analysis. Finally, we analysed regional hypometabolism in patients with Alzheimer's disease and FTLD in comparison with subjects with subjective cognitive impairment as a control group in our cohort. For details of the methods and results, see Dukart *et al*. (2010). Age was again included as a covariate, and cerebellar normalization of [^{18}F]fluorodeoxyglucose-PET data was applied.

Results

Executive functions in early dementia and its pre-stages

Table 1 illustrates neuropsychological test results for the various subject groups. Groups differed significantly with respect to the Stroop task, fluency, Zoo Tests and Key Search of the BADS (one-way ANOVA). Performance in the Action Program of the BADS did not show differences between groups. A *post hoc* analysis was conducted for subjects with subjective cognitive impairment, Alzheimer's disease and FTLD groups with unpaired two-tailed *post hoc* Student's *t*-tests, corrected for multiple comparisons according to Bonferroni, and adjusted for inequality of variance if necessary. We excluded patients with other dementia subtypes due to the lack of specificity of the dementia syndrome and subjects with mild cognitive impairment due to their small number from this analysis.

Both dementia groups showed impairments in the Stroop task in comparison with subjects with subjective cognitive impairment (Alzheimer's disease: $T = -3.7$, df = 8.3, $P = 0.02$; FTLD: $T = -3.2$, df = 7.2, $P = 0.04$), whereas there were no significant differences between patients with dementia ($T = -0.3$, df = 15, $P = 0.78$). The same was the case for fluency (subjective cognitive impairment versus Alzheimer's disease: $T = 4.0$, df = 15, $P = 0.003$; versus FTLD: $T = 3.2$, df = 11, $P = 0.03$; Alzheimer's disease versus FTLD: $T = 0.7$, df = 20, $P = 1.0$) and Key Search (subjective cognitive impairment versus Alzheimer's disease: $T = 3.0$, df = 23.9, $P = 0.02$; versus FTLD: $T = 5.2$, df = 17, $P = 0.001$; Alzheimer's disease versus FTLD: $T = 2.2$, df = 23, $P = 0.12$). Regarding both Zoo Tests, patients with Alzheimer's disease were more impaired than subjects with subjective cognitive impairment (Zoo 1: $T = 7.3$, df = 11.1, $P = 0.001$; Zoo 2: $T = 3.3$, df = 14, $P = 0.02$), whereas there was no difference between subjective cognitive impairment and FTLD (Zoo 1: $T = 1.2$, df = 14.1, $P = 0.78$; Zoo 2: $T = 1.0$, df = 16, $P = 0.99$). For the Zoo 1 test, there was a significant difference between Alzheimer's disease and FTLD ($T = -3.6$, df = 8.8, $P = 0.02$), and for the Zoo 2 test, there was a trend regarding this group difference ($T = -2.4$, df = 20.7, $P = 0.08$). Summing up the behavioural results, executive deficits were higher in both kinds of early dementia in comparison to subjects with subjective cognitive impairment for five out of the six tests applied, whereas the only difference between Alzheimer's disease and FTLD was worse performance for the Zoo Test of the BADS in Alzheimer's disease.

Although almost all results for executive tests correlated with each other ($P < 0.05$; correlation according to Pearson across the whole cohort of 54 subjects, two-tailed; except Zoo 1 and Key Search $P = 0.16$, Zoo 1 and Action Program, Zoo 2 and Stroop $P = 0.4$), executive and behavioural deficits were dissociated. Out of apathy, disinhibition and eating disorders, the most frequent behavioural disorders in early FTLD, Alzheimer's disease and also in our cohort (Schroeter *et al*., 2011), only apathy correlated with performance in the Stroop task ($r = 0.49$, $P = 0.005$) and fluency (Supermarket Test) ($r = -0.37$, $P = 0.02$). All other correlations did not reach significant values ($P > 0.1$). The same was the case for depression.

Correlation between executive deficits and reductions in brain glucose utilization

Results for the correlation analysis, including all 54 subjects, are illustrated in Figs 1 and 2, and Tables 2 and 3.

Stroop task

Impairment in behavioural performance related to Stroop interference was correlated with hypometabolism in the left inferior frontal junction and posterior superior and middle frontal gyrus (BA8/9).

Fluency task

Reduced semantic fluency was associated with hypometabolism again in the left hemisphere, namely the inferior frontal junction (BA6/8/44), all frontal gyri (BA8/9, 44–47), anterior and middle insula and deep frontal operculum (BA14/15). Moreover, the analysis revealed clusters in the inferior temporal gyrus and sulcus (BA20/21), caudate head and lentiform nucleus.

Behavioural Assessment of the Dysexecutive Syndrome

Impairments on the Action Program of the BADS were correlated with reduced brain glucose metabolism in a left hemispheric

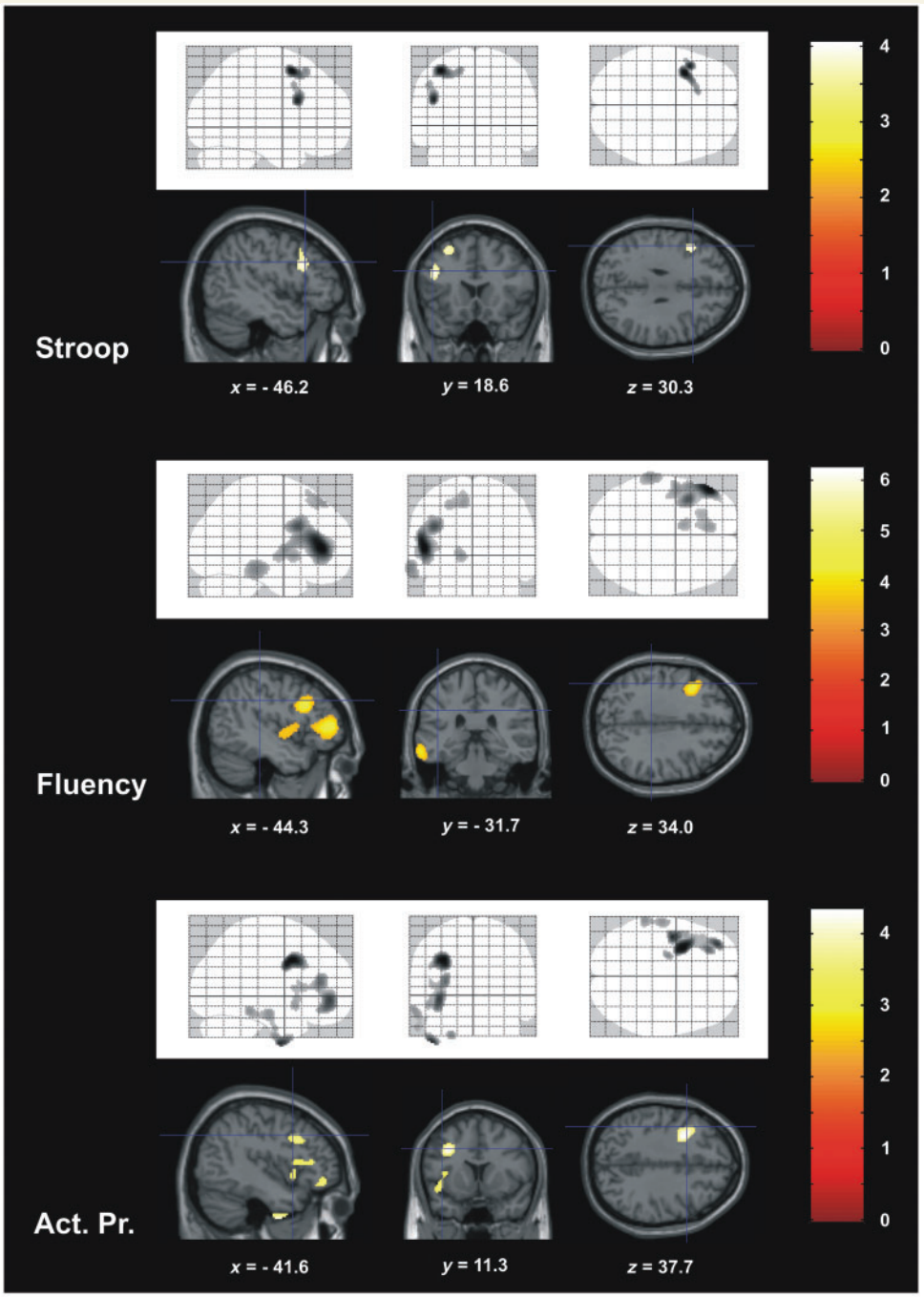

Figure 1 Correlation between reductions in brain glucose utilization and executive dysfunctions—Stroop Test (Stroop), Category Fluency (Fluency) and subtest Action Program (Act. Pr.) of the BADS. Brain sections (location illustrated by crosshairs) visualize relevant neural clusters. Age as covariate. $P < 0.001$ uncorrected. Left is left. Colour scales represent *t*-values.

network (Fig. 1, Table 3). This contained the inferior frontal junction (BA6/8/44), pars orbitalis and triangularis of the inferior frontal gyrus (BA10/45–47), the anterior insula (BA15/16), anterior and lateral orbital gyrus (BA11/12), inferior temporal pole and sulcus (BA20/21/37/38) and the parahippocampal gyrus (BA20). Deficits in the subtest Key Search of the BADS were associated with regional hypometabolism in the left inferior frontal junction (BA6/8/44), anterior insula (BA15/16), inferior frontal gyrus, namely the pars triangularis and orbitalis (BA11/45/47), lateral and anterior orbital gyrus (BA11/12), left inferior temporal pole and gyrus (BA20/21/38) (Fig. 2, Table 3).

In contrast to the aforementioned tests that were mainly related to the left lateral prefrontal lobe, both Zoo Map Tests showed a different pattern, mainly involving the parietal cortex bilaterally. More specifically, the Zoo Map Test Part 1 was related to hypometabolism bilaterally in the posterior inferior parietal

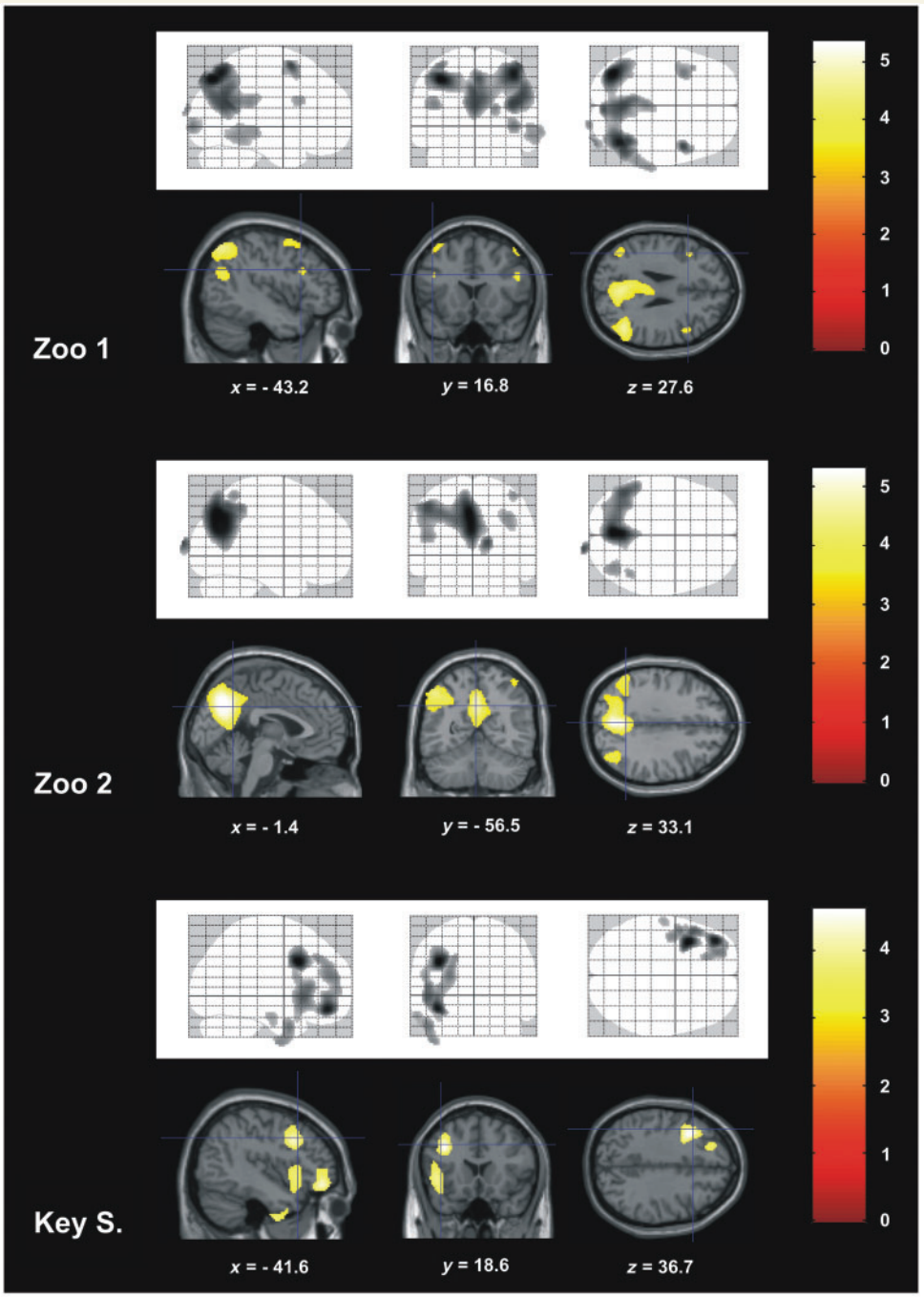

Figure 2 Correlation between reductions in brain glucose utilization and executive dysfunctions—Subtests Zoo Map (Zoo; Part 1 and 2) and Key Search (Key S.) of the BADS. Brain sections (location illustrated by crosshairs) visualize relevant neural clusters. Age as covariate. $P < 0.001$ uncorrected. Left is left. Colour scales represent *t*-values.

lobule (BA 7/39), inferior precuneus (BA7), posterior cingulate gyrus/retrosplenial cortex/parieto-occipital fissure (BA18/19/23/29/30), right temporoparietal junction area (BA22), posterior middle temporal gyrus (BA21/37), left posterior inferior temporal sulcus/anterior occipital sulcus (BA19/37/39) and right lateral and superior occipital gyri (BA19). Additionally, as in the former tasks, the inferior frontal junction (BA6/8/44) and other frontal regions, namely the posterior middle frontal gyri/frontal eye fields (BA6/8), were bilaterally involved. In contrast, areas showing hypometabolism in correlation with the Zoo Map Test Part 2 were limited to parietal areas. The clusters spread across the left posterior inferior parietal lobule (BA 7/39), bilateral inferior precuneus (BA7), parieto-occipital fissure (BA18/19/23/31), left temporoparietal junction area (BA22), right angular gyrus (BA39), the anterior horizontal part of the intraparietal sulcus (BA7/39) and superior occipital gyrus (BA18/19).

Table 2 Correlation between reductions in brain glucose utilization and executive dysfunctions—Stroop Test and category fluency

Anatomical regions	Laterality	Coordinates			T-score	Z-score	Cluster size
		x	y	z			
Stroop Test							
Left posterior superior and middle frontal gyrus (BA8/9)	Left	−36	10	58	4.04	3.57	297
	Left	−16	24	58	3.58	3.23	
Left inferior frontal junction area (BA6/8/44)	Left	−44	16	28	3.93	3.49	162
	Left	−50	12	42	3.50	3.17	
Category Fluency							
Left inferior frontal junction area (BA6/8/44), inferior frontal gyrus (BA44−47), anterior and middle insula, deep frontal operculum (BA14/15)	Left	−50	40	8	6.22	5.05	2349[a]
	Left	−40	16	30	4.96	4.27	
	Left	−52	2	6	4.02	3.61	
Left inferior temporal gyrus, inferior temporal sulcus (BA20/21)	Left	−66	−30	−14	4.20	3.74	418
Left superior and middle frontal gyrus (BA8/9)	Left	−10	40	54	3.90	3.52	277
	Left	−24	32	52	3.62	3.31	
Left caudate (head), lentiform nucleus	Left	−12	10	0	3.83	3.47	144

Age was included as a covariate in the analysis. Cluster size is reported in voxels, voxel size = 2 × 2 × 2 mm. $P_{(uncorrected)} < 0.001$, equivalent to Stroop Test $T = 3.40$, Category Fluency $T = 3.35$.

a $P < 0.01$ corrected for multiple comparisons on the cluster level. Clusters >30 voxels are reported. Coordinates are in MNI space.

After correction for multiple comparisons on the cluster level with $P < 0.05$, the analysis confirmed relevant clusters for fluency, both Zoo Map Tests, and the Key Search subtest of the BADS (Tables 2 and 3). The clusters included the inferior frontal junction with respect to fluency and Key Search of the BADS, whereas for the Stroop test, Action Program and Zoo Map Test Part 1, the cluster in the inferior frontal junction was presumably too small.

Executive deficits and glucose utilization: conjunction analysis

To isolate the brain region most consistently involved in executive deficits, we conducted a conjunction analysis across the neural correlates of the various executive tasks. This analysis included the Stroop and fluency test, and the subtests Action Program, Key Search and Zoo Map Test Part 1 of the BADS. Part 2 of the Zoo Map Test was excluded from this analysis, since patients are simply asked to follow a pre-specified order of steps, and accordingly, executive functions are less involved. This assumption was supported by the absence of a correlation with frontal regions for the latter test. Figure 3 illustrates the results of the conjunction analysis. All five executive tests were related to hypometabolism in one prefrontal region, namely the left inferior frontal junction (BA6/8/44). This finding was observed for both types of conjunction analyses. In the map of overlapping regions, there was $z > 3.1$ ($P < 0.001$) for all five executive functions in (maximum) −44, 17, 29 (Fig. 3A). The map of minimum *z*-values for all executive functions (Nichols *et al.*, 2004) showed its maximum in the same voxel (−42, 20, 30) (Fig. 3B). Most strikingly, these results coincided anatomically with a recent systematic and quantitative meta-analysis (Derrfuss *et al.*, 2005), which used the activation likelihood estimate method to investigate the neural correlates of Stroop and switching in functional MRI studies (Fig. 3C; respective coordinates of maxima after transformation to MNI space −43, 7, 32 and −43, 7, 38).

Dissociation between executive and behavioural deficits in early dementia

We compared the results of our conjunction analysis with the results of our previous study that systematically investigated the neural correlates of behavioural disorders in exactly the same cohort with the same method ([^{18}F]fluorodeoxyglucose-PET) (Schroeter *et al.*, 2011). This study isolated three relevant behavioural disorders, namely apathy, disinhibition and eating disorders, out of all components of the Neuropsychiatric Inventory that correlated with regional brain hypometabolism. The comparison of the results from our multiple regression analysis including all three behavioural disorders (Fig. 3D) with the results of our present conjunction analysis (Fig. 3A and B) revealed no overlapping brain regions. Hypometabolism in the inferior frontal junction seems to be specifically related to executive dysfunctions, but not related to behavioural disorders in our study cohort. Results agree with the observation that executive deficits hardly correlated with behavioural disorders in the study group.

Regional reductions in glucose metabolism in early dementia: group comparisons

Finally, we analysed regional hypometabolism in patients with Alzheimer's disease and FTLD in our cohort by comparing them separately with control subjects (subjective cognitive impairment) (Fig. 4). Interestingly, the analysis revealed regionally overlapping reductions in glucose utilization for both Alzheimer's disease and FTLD mainly in the left inferior frontal junction (cluster size 1477 voxels; maximum in MNI space −44, 4, 60), and additionally, but

Table 3 Correlation between reductions in brain glucose utilization and executive dysfunctions—BADS

Anatomical regions	Laterality	Coordinates			T-score	Z-score	Cluster size
		x	y	z			
BADS Action Program							
Left inferior frontal junction area (BA6/8/44)	Left	−32	8	38	4.32	3.86	522
Left inferior temporal pole (BA20/38)	Left	−44	−4	−48	4.11	3.70	136
Left inferior frontal gyrus, pars orbitalis and triangularis (BA10/45−47), anterior insula (BA15/16), anterior and lateral orbital gyrus (BA11/12)	Left	−36	48	−4	4.00	3.62	789
	Left	−30	38	14	3.77	3.45	
	Left	−46	12	−8	3.49	3.22	
Left parahippocampal gyrus (BA20)	Left	−24	−10	−40	3.58	3.30	48
Left inferior temporal sulcus (BA20/21/37)	Left	−62	−36	−16	3.57	3.29	226
	Left	−62	−16	−18	3.55	3.27	
	Left	−60	−10	−34	3.45	3.19	
BADS Zoo Map Test (Part 1)							
Bilateral posterior inferior parietal lobule (BA 7/39), inferior precuneus (BA7), posterior cingulate gyrus/retrosplenial cortex/ parieto-occipital fissure (BA18/19/23/29/30), right temporoparietal junction area (BA22)	Left	−36	−74	48	5.33	4.58	8402[a]
	Right	42	−66	54	5.10	4.43	
	Right	42	−60	24	4.70	4.14	
Right posterior middle frontal gyrus/frontal eye field (BA6/8)	Right	46	8	62	4.61	4.08	172
Left posterior middle frontal gyrus/frontal eye field (BA6/8)	Left	−38	8	62	4.05	3.67	245
Right lateral occipital gyrus (BA19)	Right	40	−96	0	4.00	3.63	140
Left posterior inferior temporal sulcus/anterior occipital sulcus (BA19/37/39)	Left	−42	−64	22	3.94	3.58	250
Right superior occipital gyrus (BA19)	Right	22	−102	18	3.87	3.53	51
Right posterior middle temporal gyrus (BA21/37)	Right	62	−46	−10	3.77	3.45	632
	Right	70	−32	−4	3.74	3.43	
Right inferior frontal junction area (BA6/8/44)	Right	50	16	26	3.70	3.39	63
Left inferior frontal junction area (BA6/8/44)	Left	−42	20	26	3.68	3.38	32
BADS Zoo Map Test (Part 2)							
Left posterior inferior parietal lobule (BA 7/39), bilateral inferior precuneus (BA7), parietooccipital fissure (BA18/19/23/31), left temporoparietal junction area (BA22)	Left	−4	−70	42	5.28	4.52	6451[a]
	Left	−48	−60	48	4.50	3.98	
	Left	−48	−66	20	3.87	3.51	
Right superior occipital gyrus (BA18/19)	Right	16	−106	14	4.47	3.96	138
Right angular gyrus (BA39)	Right	38	−72	36	3.85	3.50	394
Right intraparietal sulcus, anterior horizontal part (BA7/39)	Right	44	−52	62	3.77	3.44	75
BADS Key Search							
Left inferior frontal junction area (BA6/8/44), anterior insula (BA15/16), inferior frontal gyrus, pars triangularis and orbitalis (BA11/45/47), lateral and anterior orbital gyurs (BA11/12)	Left	−38	16	36	4.60	4.11	2890[a]
	Left	−38	46	−14	4.46	4.01	
	Left	−48	20	−2	3.97	3.64	
Left inferior temporal pole (BA20/38)	Left	−48	6	−32	3.75	3.46	368
	Left	−44	−2	−46	3.66	3.39	
Left inferior temporal gyrus (BA20/21)	Left	−60	−12	−22	3.47	3.24	98

Age was included as a covariate in the analysis. Cluster size is reported in voxels, voxel size = 2 × 2 × 2 mm. $P_{(uncorrected)} < 0.001$, equivalent to Zoo Map (Part 1) $T = 3.32$, Zoo Map (Part 2) $T = 3.33$, Key Search $T = 3.30$, Action Program $T = 3.33$.
a $P < 0.01$ corrected for multiple comparisons on the cluster level. Clusters >30 voxels are reported. Coordinates are in MNI space.

to a smaller extent, in the left inferior temporal (514; −62, −28, −18) and angular gyrus (228; −56, −62, 36).

Discussion

Executive functions and the inferior frontal junction area

Our study systematically investigated the neural correlates of executive functions by correlating reductions in glucose utilization with executive deficits in early dementia and its pre-stages as measured by classical tests, such as Stroop and fluency tasks and recently developed tasks investigating executive functions in a context more relevant to daily life, namely the BADS. In agreement with our hypothesis, executive deficits were mainly associated with prefrontal hypometabolism. Most interestingly, we identified the inferior frontal junction (BA 6/8/44) as the most consistently relevant region across all executive tasks. Miyake suggested that executive control may be best conceptualized as comprising at least three different component processes: working memory, task switching and inhibitory control. Indeed, two comprehensive systematic and quantitative meta-analyses of functional MRI studies using the activation likelihood estimate approach have identified the inferior frontal junction as being

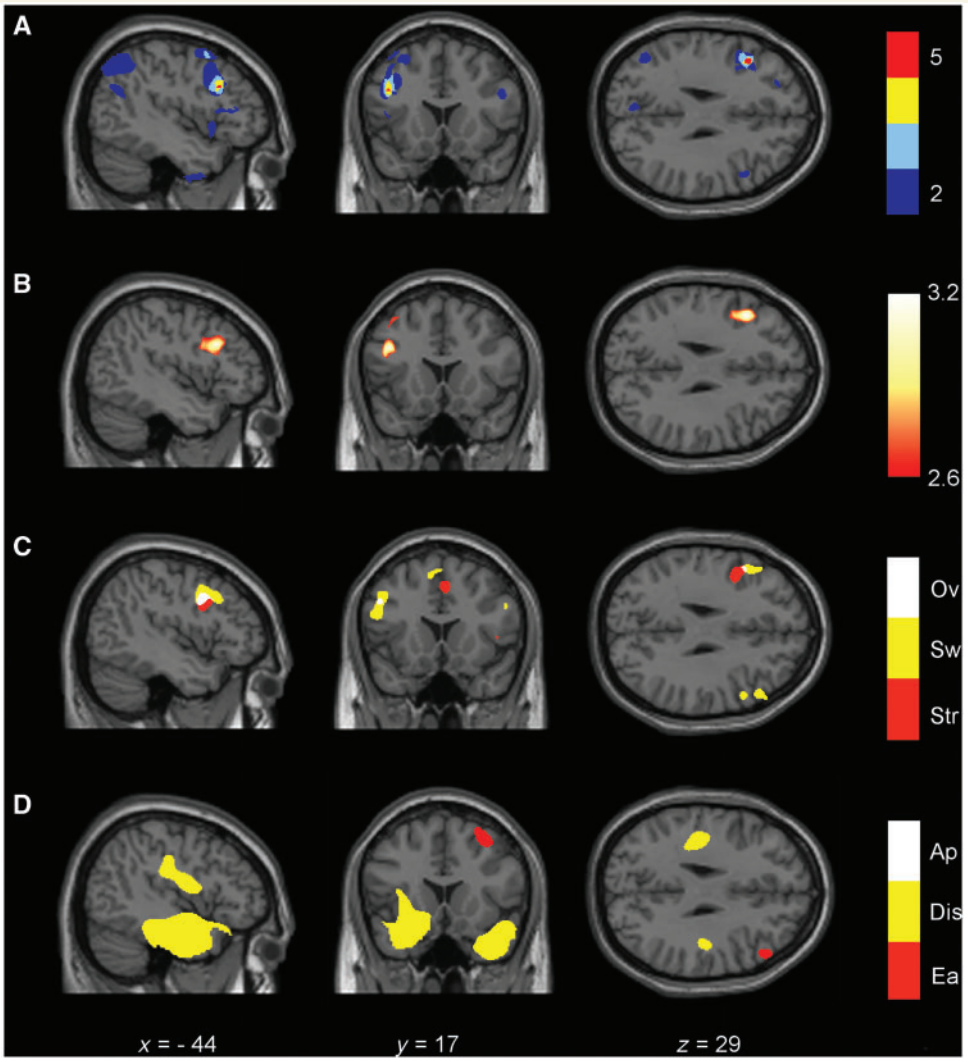

Figure 3 Conjunction analyses. Brain regions that showed consistently reduced glucose metabolism in association with executive deficits. (**A**) Overlap of *t*-maps of all five tests. Maximum is located in the vicinity of the inferior frontal junction area (i.e. in this region, *t*-values of all statistical tests are significant with voxelwise $P < 0.001$). Scale represents number of overlapping tests. (**B**) Minimum *z*-score for all five executive function tests which corresponds to a conjunction analysis in the sense of a logical 'AND'. Maximum of the resulting map of *z*-values is again located in the vicinity of the inferior frontal junction. (**C**) Results of the meta-analysis of studies investigating Stroop (Str) and Switch (Sw) tasks with functional MRI transformed into the MNI space using the unified segmentation approach (Ov = overlap; Derrfuss *et al*., 2005). (**D**) Results of our previous study with exactly the same cohort investigating the neural correlates of behavioural disorders in dementia—correlation between reduced glucose metabolism and apathy (Ap), disinhibition (Dis) and eating disorders (Ea) (Schroeter *et al*., 2011).

relevant for the three component processes (Brass *et al*., 2005; Derrfuss *et al*., 2005; Christ *et al*., 2009). In sum, our study indirectly supports Miyake *et al's* (2000) assumption that executive control comprises the three component processes and the relevance of the inferior frontal junction.

The inferior frontal junction is located at the junction of the inferior frontal sulcus and the inferior precentral sulcus (Derrfuss *et al*., 2009). If one follows the assumption that the border zone between the dorso- and ventrolateral prefrontal cortex is constituted by the inferior frontal sulcus, the inferior frontal junction covers both areas (Sakai *et al*., 2008). Others, based on monkey studies, have argued that the border zone is constituted by the middle frontal sulcus (as the analogue of the monkey's sulcus principalis)—a region within the middle frontal gyrus (Petrides and Pandya, 1999; see Fig. 3 in Petrides and Pandya, 2002). In this case, the inferior frontal junction would be located in the ventrolateral prefrontal cortex and one might conclude from our data that executive functions in early dementia are not related to the dorsolateral prefrontal cortex. However, if the results for the single executive tests are examined instead the conjunction analysis, test performance also correlated with hypometabolism in the dorsolateral prefrontal cortex according to its second definition (at least for three out of the five relevant 'frontal' neuropsychological tests: Stroop, fluency, Zoo 1 task; Figs 1–3,

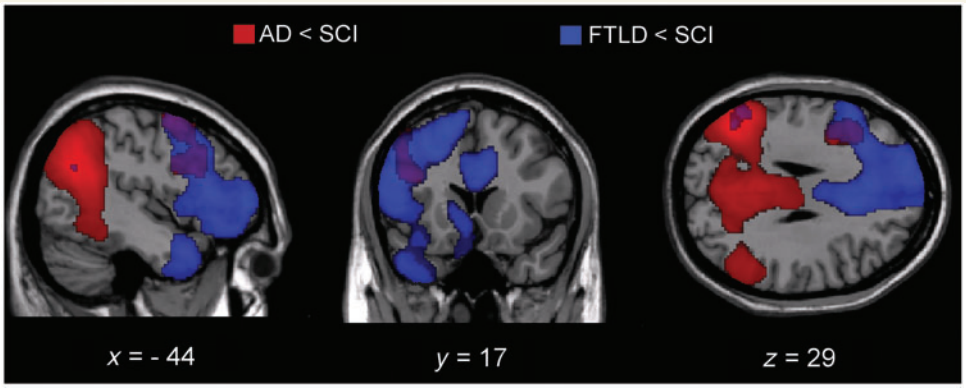

Figure 4 Group comparison—brain regions that showed reduced glucose metabolism in Alzheimer's disease (AD, red) and frontotemporal lobar degeneration (FTLD, blue) in comparison with subjects with subjective cognitive impairment (SCI). Overlap (purple) includes the left inferior frontal junction area. Age as covariate, $P < 0.001$ uncorrected, extent threshold of 30 voxels. Left is left. Note that coordinates in MNI space are identical to Fig. 3.

Tables 2 and 3). These effects disappeared in the conjunction analysis, presumably due to a high regional variability.

Executive deficits are related to the inferior frontal junction area in early dementia

In the following, we discuss our results in the context of executive deficits in dementia. Interestingly, inhibitory functions that are relevant in the Stroop task are the first component of the attentional system to become impaired after amnestic symptoms in early Alzheimer's disease (Amieva *et al*., 2004; Hodges, 2006). Thereafter, divided attention as tested with switching tasks is affected (Baddley *et al*., 2001). Breakdown in higher order cognitive (executive) abilities is virtually always present in patients with established Alzheimer's disease, in agreement with impairments of the frontal lobes (Perry and Hodges, 1999; Hodges, 2006; Schroeter *et al*., 2009).

FTLD, particularly FTD, is neuropsychologically characterized by deficits in executive function tests, namely Stroop, Trail Making, Wisconsin Card Sorting and verbal fluency tests (Harciarek and Jodzio, 2005). Recent studies suggested that these executive dysfunctions may occur in tau mutation carriers with inherited FTD even decades before clinical manifestation (Geschwind *et al*., 2001), and may predict the progression of the disease (Hornberger *et al*., 2008). Executive deficits are less frequent in semantic dementia, another subtype of FTLD (Perry and Hodges, 2000; Harciarek and Jodzio, 2005). Our study did not include the third subtype of FTLD—progressive non-fluent aphasia (Neary *et al*., 1998). Although it has been suggested that patients with FTD are more impaired in executive function tasks requiring planning than patients with Alzheimer's disease, general attentional/executive differences between FTD and Alzheimer's disease are a controversial issue (Perry and Hodges, 2000; Harciarek and Jodzio, 2005; Collette *et al*., 2007; Giovagnoli *et al*., 2008) and could not be confirmed in comprehensive meta-analyses (Hutchinson and Mathis, 2007).

Our study suggests that attentional/executive deficits in early Alzheimer's disease and FTLD are associated with dysfunction in the inferior frontal junction. Note that the group comparison of our patient cohorts versus control subjects revealed hypometabolism in the inferior frontal junction in both Alzheimer's disease and FTLD. Results are in agreement with other studies reporting prefrontal atrophy or hypometabolism/hypoperfusion in Alzheimer's disease and FTLD/FTD (Thompson *et al*., 2003; Schroeter *et al*., 2007*c*, 2008, 2009; Schroeter and Neumann, 2011), and (mainly lateral) prefrontal correlation of imaging data with performance in classical executive function tests in FTLD (FTD and semantic dementia), Alzheimer's disease and mild cognitive impairment (Salmon *et al*., 2006, 2008, 2009; Teipel *et al*., 2006; Bracco *et al*., 2007; Grossman *et al*., 2007; Kramer *et al*., 2007; Guedj *et al*., 2008; Fine *et al*., 2009; Huey *et al*., 2009; Pa *et al*., 2009; Nishi *et al*., 2010).

Although most of the executive tests showed a main focus in the left lateral prefrontal lobe, the Zoo Map Test mainly involved the parietal cortex bilaterally. This test poses considerable demands on visuospatial constructional abilities and spatial navigation, which are impaired in patients with Alzheimer's disease (Hodges, 2006) and have been related to the inferior parietal lobules extending into the intraparietal sulcus and the precuneus—regions that are particularly affected in Alzheimer's disease (Cavanna and Trimble, 2006; Schroeter *et al*., 2009). This explanation is further supported by the observation that patients with Alzheimer's disease were more impaired in both parts of the Zoo Map Test than the other dementia subgroups in our cohort—whereas for the other executive tests, we did not find group-specific differences. Interestingly, the difference between Alzheimer's disease and FTLD disappeared when we compared the difference between performance in Part 1 and Part 2 of the Zoo Map Test, isolating more strictly executive functions (as discussed above) than those involved in the single tests (-5.1 ± 3.4 versus -2.6 ± 3.5; $T = -1.7$, $df = 21$, $P > 0.1$; two-tailed unpaired Student's *t*-test).

Executive deficits in early dementia and the frontomedian cortex

Surprisingly, we did not detect a correlation between hypometabolism in frontomedian regions and executive functions, although the posterior medial frontal cortex is involved in performance monitoring in relation to anticipated reward (Ridderinkhof *et al*., 2004), and activation in this brain region has been related to the three component processes of executive control (Miyake *et al*., 2000; Christ *et al*., 2009). This result might be related to the fact that the focus of frontomedian impairments in Alzheimer's disease and FTLD/FTD as shown in comprehensive activation likelihood estimate meta-analyses (Schroeter *et al*., 2007*c*, 2008, 2009; Schroeter and Neumann, 2011) is located more anteriorly (anterior medial frontal cortex and pregenual anterior cingulate gyrus) than functional neural correlates for the detection of response conflict, errors and unfavourable outcomes (Ridderinkhof *et al*., 2004) and the three component processes of executive control (Christ *et al*., 2009).

In sum, our study shows that patients with both early Alzheimer's disease and FTLD are impaired in executive functions, and that executive dysfunctions are related to the inferior frontal junction. Inferior frontal junction dysfunction might impair the three component processes of cognitive control, working memory, task switching and inhibitory control (Miyake *et al*., 2000; Derrfuss *et al*., 2005; Christ *et al*., 2009), and finally lead to impairment in all executive tests as applied in our study. The mechanisms of this impairment, namely the specifically involved cognitive processes, need to be investigated in future studies.

It is well known that the BADS captures essential aspects of executive abilities that are relevant to daily living (Wilson *et al*., 1996; Strauss *et al*., 2006). Indeed, results in this test battery were, on average, more closely related to dementia severity (Clinical Dementia Rating Scale) than the other classical executive tests in our cohort (Action Program $r = -0.56$, Zoo Map Test 1 and 2 $r = -0.53$, -0.65, $P < 0.001$; Key Search $r = -0.38$, $P = 0.01$; Stroop and fluency task $r = 0.48$, -0.36, $P = 0.005$, 0.03, respectively). One might also conclude that impairment of the inferior frontal junction influence, deficits in every day life in early dementia.

Dissociation between executive and behavioural deficits in early dementia

Another aim of the present study was to compare the neural correlates of executive deficits and behavioural disorders in early dementia, as it is widely known that both are related to the frontal lobes (Carter *et al*., 1998; Derrfuss *et al*., 2004, 2005; Ridderinkhof *et al*., 2004; Rosen *et al*., 2005; Raczka *et al*., 2010). Accordingly, we compared our results with those of our previous study systematically investigating the neural correlates of behavioural disorders in exactly the same subjects with the same imaging method (Schroeter *et al*., 2011). Our results suggest that the inferior frontal junction is specifically related to executive dysfunctions and not behavioural deficits in early dementia, as the second conjunction analysis did not reveal any overlapping brain regions and executive deficits hardly correlated with behavioural disorders in our cohort.

Limitations of the study

Finally, the limitations of the study must be acknowledged. As already discussed in the 'Introduction', we included a diverse group of subjects ranging from subjects with various kinds of early dementia to its prodromal stages, subjective cognitive impairment and mild cognitive impairment. We decided to involve such a study cohort, because we were interested in the neural correlates of executive functions *per se*, and we wanted to include a large variance of symptom severity and accordingly increase statistical power—an approach that has been applied successfully in other studies (Rosen *et al*., 2005; Rankin *et al*., 2006). In fact, we were able to systematically reveal the correlates of executive impairments in early dementia. Since both FTLD and Alzheimer's disease showed comparable deficits in executive functions, regional hypometabolism in the inferior frontal junction and the dementia subgroups did not differ regarding severity, education and disease duration, one might assume that our results are relevant for both early Alzheimer's disease and FTLD. However, the comparison with the subjective cognitive impairment group could not be performed for patients with dementias other than Alzheimer's disease/FTLD, because this dementia subgroup consisted of diverse dementia subtypes. Regarding the trade-off between specificity for dysexecutive syndromes and for dementia subtypes, we elected to give preference to the former, as we were interested in the specific neural correlates for executive deficits *per se*. One might suggest conducting the same kind of study to determine the role of the inferior frontal junction in executive function in healthy subjects. However, performing [^{18}F]fluorodeoxyglucose-PET in this cohort is almost impossible due to ethical issues (radiation exposure). Furthermore, for the BADS one might expect ceiling effects in control subjects, because they are not impaired in executive functions. One might further criticize the fact that we did not correct for atrophy. However, most studies that have performed voxel-based atrophy correction of resting glucose metabolism have reported a relative independence of metabolism from brain atrophy, particularly for localization of maxima (Bracco *et al*., 2007; Drzezga *et al*., 2008)—a finding that could be replicated in our cohort (Dukart *et al*., 2010).

Conclusion

Our study examined the neural correlates of executive functions by correlating respective test scores with reductions in glucose utilization in early dementia and its prodromal stages. The analysis consistently isolated one region in the left lateral prefrontal cortex, namely the inferior frontal junction area, across various neuropsychological tests. Results underline the importance of this brain region for cognitive control processes in general, and for executive deficits in early dementia in particular.

Acknowledgements

The authors thank the PET and cyclotron staff at the Department of Nuclear Medicine and the staff at the Day Clinic for Cognitive Neurology at the University of Leipzig for help in data acquisition, and Jan Derrfuss and Jürgen Dukart for providing the results of their studies. The authors are most grateful to all subjects participating in the study.

Funding

LIFE - Leipzig Research Centre for Civilization Diseases at the University of Leipzig (to M.L.S., H.B., A.V. and O.S.). European Union, European Regional Development Fund (ERDF) and Free State of Saxony within the framework of the Excellence Initiative to LIFE. German Federal Ministry of Education and Research (BMBF) - German FTLD consortium (to M.L.S.).

References

Amieva H, Phillips LH, Della Sala S, Henry JD. Inhibitory functioning in Alzheimer's disease. Brain 2004; 127: 949–64.

Apostolova LG, Steiner CA, Akopyan GG, Dutton RA, Hayashi KM, Toga AW, et al. Three-dimensional gray matter atrophy mapping in mild cognitive impairment and mild Alzheimer disease. Arch Neurol 2007; 64: 1489–95.

Bäckman L, Jones S, Berger AK, Laukka EJ, Small BJ. Multiple cognitive deficits during the transition to Alzheimer's disease. J Intern Med 2004; 256: 195–204.

Bäckman L, Jones S, Berger AK, Laukka EJ, Small BJ. Cognitive impairment in preclinical Alzheimer's disease: a meta-analysis. Neuropsychology 2005; 19: 520–31.

Baddeley AD, Baddeley HA, Bucks RS, Wilcock GK. Attentional control in Alzheimer's disease. Brain 2001; 124: 1492–508.

Barthel H, Gertz HJ, Dresel S, Peters O, Bartenstein P, Buerger K, et al. Cerebral amyloid-ß PET with florbetaben (^{18}F) in patients with Alzheimer's disease and healthy controls: a multicentre phase 2 diagnostic study. Lancet Neurol 2011; 10: 424–35.

Blennow K, de Leon MJ, Zettenberg H. Alzheimer's disease. Lancet 2006; 368: 387–403.

Boeve BF, Lang AE, Litvan I. Corticobasal degeneration and its relationship to progressive supranuclear palsy and frontotemporal dementia. Ann Neurol 2003; 54 (Suppl. 5): S15–9.

Bracco L, Bessi V, Piccini C, Mosconi L, Pupi A, Sorbi S. Metabolic correlates of executive dysfunction. Different patterns in mild and very mild Alzheimer's disease. J Neurol 2007; 254: 1052–65.

Brass M, Derrfuss J, Forstmann B, von Cramon D. The role of the inferior frontal junction area in cognitive control. Trends Cogn Sci 2005; 9: 314–6.

Burgess PW. Theory and methodology in executive function research. In: Rabbitt P, editor. Methodology of frontal and executive function. East Sussex: Psychology Press; 1997. p. 81–116.

Carter CS, Braver TS, Barch DM, Botvinick MM, Noll D, Cohen JD. Anterior cingulate cortex, error detection, and the online monitoring of performance. Science 1998; 280: 747–9.

Cavanna AE, Trimble MR. The precuneus: a review of its functional anatomy and behavioural correlates. Brain 2006; 129: 564–83.

Cerhan JH, Ivnik RJ, Smith GE, Tangalos EC, Petersen RC, Boeve BF. Diagnostic utility of letter fluency, category fluency, and fluency difference scores in Alzheimer's disease. Clin Neuropsychol 2002; 16: 35–42.

Chen P, Ratcliff G, Belle SH, Cauley JA, DeKosky ST, Ganguli M. Patterns of cognitive decline in presymptomatic Alzheimer disease: a prospective community study. Arch Gen Psychiatry 2001; 58: 853–8.

Christ SE, Van Essen DC, Watson JM, Brubaker LE, McDermott KB. The contributions of prefrontal cortex and executive control to deception: evidence from activation likelihood estimate meta-analyses. Cereb Cortex 2009; 19: 1557–66.

Collette F, Amieva H, Adam S, Hogge M, Van der Linden M, Fabrigoule C, et al. Comparison of inhibitory functioning in mild Alzheimer's disease and frontotemporal dementia. Cortex 2007; 43: 866–74.

Crawford JR, Henry JD. Assessment of executive dysfunction. In: Halligan P, Wade DT, editors. Effectiveness of rehabilitation for cognitive deficits. Oxford: University Press; 2005. p. 233–46.

Cummings JL. The neuropsychiatric inventory: assessing psychopathology in dementia patients. Neurology 1997; 48: S10–6.

Derrfuss J, Brass M, Neumann J, von Cramon DY. Involvement of the inferior frontal junction in cognitive control: meta-analyses of switching and Stroop studies. Hum Brain Mapp 2005; 25: 22–34.

Derrfuss J, Brass M, von Cramon DY. Cognitive control in the posterior frontolateral cortex: evidence from common activations in task coordination, interference control, and working memory. NeuroImage 2004; 23: 604–12.

Derrfuss J, Brass M, von Cramon DY, Lohmann G, Amunts K. Neural activations at the junction of the inferior frontal sulcus and the inferior precentral sulcus: interindividual variability, reliability, and association with sulcal morphology. Hum Brain Mapp 2009; 30: 299–311.

Drzezga A, Grimmer T, Henriksen G, Stangier I, Perneczky R, Diehl-Schmid J, et al. Imaging of amyloid plaques and cerebral glucose metabolism in semantic dementia and Alzheimer's disease. NeuroImage 2008; 39: 619–33.

Dubois B, Feldman HH, Jacova C, DeKosky ST, Barberger-Gateau P, Cummings J, et al. Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. Lancet Neurol 2007; 6: 734–46.

Dukart J, Mueller K, Horstmann A, Barthel H, Möller HE, Villringer A, et al. Combined evaluation of FDG-PET and MRI improves detection and differentiation of dementia. PLoS One 2011; 6: e18111.

Dukart J, Mueller K, Horstmann A, Vogt B, Frisch S, Barthel H, et al. Differential effects of global and cerebellar normalization on detection and differentiation of dementia in FDG-PET studies. NeuroImage 2010; 49: 1490–5.

Fine EM, Delis DC, Dean D, Beckman V, Miller BL, Rosen HJ, et al. Left frontal lobe contributions to concept formation: a quantitative MRI study of performance on the Delis-Kaplan Executive Function System Sorting Test. J Clin Exp Neuropsychol 2009; 31: 624–31.

Geschwind DH, Robidoux J, Alarcón M, Miller BL, Wilhelmsen KC, Cummings JL, et al. Dementia and neurodevelopmental predisposition: cognitive dysfunction in presymptomatic subjects precedes dementia by decades in frontotemporal dementia. Ann Neurol 2001; 50: 741–6.

Giovagnoli AR, Erbetta A, Reati F, Bugiani O. Differential neuropsychological patterns of frontal variant frontotemporal dementia and Alzheimer's disease in a study of diagnostic concordance. Neuropsychologia 2008; 46: 1495–504.

Gorno-Tempini ML, Dronkers NF, Rankin KP, Ogar JM, Phengrasamy L, Rosen HJ, et al. Cognition and anatomy in three variants of primary progressive aphasia. Ann Neurol 2004; 55: 335–46.

Grossman M, Libon DJ, Forman MS, Massimo L, Wood E, Moore P, et al. Distinct antemortem profiles in patients with pathologically defined frontotemporal dementia. Arch Neurol 2007; 64: 1601–9.

Guedj E, Allali G, Goetz C, Le Ber I, Volteau M, Lacomblez L, et al. Frontal Assessment Battery is a marker of dorsolateral and medial frontal functions: a SPECT study in frontotemporal dementia. J Neurol Sci 2008; 273: 84–7.

Harciarek M, Jodzio K. Neuropsychological differences between frontotemporal dementia and Alzheimer's disease: a review. Neuropsychol Rev 2005; 15: 131–45.

Hodges JR. Alzheimer's centennial legacy: origins, landmarks and the current status of knowledge concerning cognitive aspects. Brain 2006; 129: 2811–22.
Hornberger M, Piguet O, Kipps C, Hodges JR. Executive function in progressive and nonprogressive behavioral variant frontotemporal dementia. Neurology 2008; 71: 1481–8.
Huey ED, Goveia EN, Paviol S, Pardini M, Krueger F, Zamboni G, et al. Executive dysfunction in frontotemporal dementia and corticobasal syndrome. Neurology 2009; 72: 453–9.
Hutchinson AD, Mathis JL. Neuropsychological deficits in frontotemporal dementia and Alzheimer's disease: a meta-analytic review. J Neurol Neurosurg Psychiatry 2007; 78: 917–28.
Jessen F, Wiese B, Bachmann C, Eifflaender-Gorfer S, Haller F, Kölsch H, et al. Prediction of dementia by subjective memory impairment: effects of severity and temporal association with cognitive impairment. Arch Gen Psychiatry 2010; 67: 414–22.
Kalbe E, Kessler J, Calabrese P, Smith R, Passmore AP, Brand M, et al. DemTect: a new, sensitive cognitive screening test to support the diagnosis of mild cognitive impairment and early dementia. Int J Geriat Psychiatry 2004; 19: 136–43.
Kramer JH, Quitania L, Dean D, Neuhaus J, Rosen HJ, Halabi C, et al. Magnetic resonance imaging correlates of set shifting. J Int Neuropsychol Soc 2007; 13: 386–92.
Laisney M, Matuszewski V, Mézenge F, Belliard S, de la Sayette V, Eustache F, et al. The underlying mechanisms of verbal fluency deficit in frontotemporal dementia and semantic dementia. J Neurol 2009; 256: 1083–94.
Libon DJ, McMillan C, Gunawardena D, Powers C, Massimo L, Khan A, et al. Neurocognitive contributions to verbal fluency deficits in frontotemporal lobar degeneration. Neurology 2009; 73: 535–42.
Loessner A, Alavi A, Lewandrowski KU, Mozley D, Souder E, Gur RE. Regional cerebral function determined by FDG-PET in healthy volunteers: normal patterns and changes with age. J Nucl Medicine 1995; 36: 1141–9.
MacLeod CM. Half a century of research on the Stroop effect: an integrative review. Psychol Bulletin 1991; 109: 163–203.
McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of department of health and human services task force on Alzheimer's disease. Neurology 1984; 34: 939–44.
McKeith IG, Galasko D, Kosaka K, Perry EK, Dickson DW, Hansen LA, et al. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies. Report of the consortium on DLB international workshop. Neurology 1996; 47: 1113–24.
Mendez MF, Ghajarania M, Perryman KM. Posterior cortical atrophy: clinical characteristics and differences compared to Alzheimer's disease. Dement Geriat Cog Disord 2002; 14: 33–40.
Miyake A, Friedman NP, Emerson MJ, Witzki AH, Howerter A, Wager TD. The unity and diversity of executive functions and their contributions to complex "frontal lobe" tasks: a latent variable analysis. Cogn Psychol 2000; 41: 49–100.
Morris JC. Clinical dementia rating: a reliable and valid diagnostic and staging measure for dementia of the Alzheimer type. Int Psychogeriatr 1997; 9: 173–8.
Neary D, Snowden JS, Gustafson L, Passant U, Stuss D, Black S, et al. Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. Neurology 1998; 51: 1546–54.
Neary D, Snowden J, Mann D. Frontotemporal dementia. Lancet Neurol 2005; 4: 771–80.
Nichols T, Brett M, Anderson J, Wager T, Poline JB. Valid conjunction inference with the minimum statistic. NeuroImage 2004; 25: 653–60.
Nishi H, Sawamoto N, Namiki C, Yoshida H, Dhin HD, Ishizu K, et al. Correlation between cognitive deficits and glucose hypometabolism in mild cognitive impairment. J Neuroimaging 2010; 20: 29–36.
Oswald WD, Fleischmann U. Das Nürnberger Alters Inventar NAI. Universität Erlangen Nürnberg: Testzentrale Stuttgart; 1986.
Pa J, Boxer A, Chao LL, Gazzaley A, Freeman K, Kramer J, et al. Clinical-neuroimaging characteristics of dysexecutive mild cognitive impairment. Ann Neurol 2009; 65: 414–23.
Perry RJ, Hodges JR. Attention and executive deficits in Alzheimer's disease: a critical review. Brain 1999; 122: 383–404.
Perry RJ, Hodges JR. Differentiating frontal and temporal variant frontotemporal dementia from Alzheimer's disease. Neurology 2000; 54: 2277–84.
Petrides M, Pandya DN. Dorsolateral prefrontal cortex: comparative cytoarchitectonic analysis in the human and the macaque brain and corticocortical connection patterns. Eur J Neurosci 1999; 11: 1011–36.
Petrides M, Pandya DN. Comparative cytoarchitectonic analysis of the human and the macaque ventrolateral prefrontal cortex and corticocortical connection patterns in the monkey. Eur J Neurosci 2002; 16: 291–310.
Rabbitt P. Introduction: methodologies and models in the study of executive function. In: Rabbitt P, editor. Methodology of frontal and executive function. East Sussex: Psychology Press; 1997. p. 1–38.
Raczka KA, Becker G, Seese A, Frisch S, Heiner S, Marschhauser A, et al. Executive and behavioral deficits share common neural substrates in frontotemporal lobar degeneration – A pilot FDG-PET study. Psychiatry Res Neuroimaging 2010; 182: 274–80.
Rankin KP, Gorno-Tempini ML, Allison SC, Stanley CM, Glenn S, Weiner MW, et al. Structural anatomy of empathy in neurodegenerative disease. Brain 2006; 129: 2945–56.
Ridderinkhof KR, Ullsperger M, Crone EA, Nieuwenhuis S. The role of the medial frontal cortex in cognitive control. Science 2004; 306: 443–7.
Rosen HJ, Allison SC, Schauer GF, Gorno-Tempini ML, Weiner MW, Miller BL. Neuroanatomical correlates of behavioural disorders in dementia. Brain 2005; 128: 2612–25.
Sakai K. Task set and prefrontal cortex. Annu Rev Neurosci 2008; 31: 219–45.
Salmon E, Kerrouche N, Herholz K, Perani D, Holthoff V, Beuthien-Baumann B, et al. Decomposition of metabolic brain clusters in the frontal variant of frontotemporal dementia. NeuroImage 2006; 30: 871–8.
Salmon E, Kerrouche N, Perani D, Lekeu F, Holthoff V, Beuthien-Baumann B, et al. On the multivariate nature of brain metabolic impairment in Alzheimer's disease. Neurobiol Aging 2009; 30: 186–97.
Salmon E, Lekeu F, Bastin C, Garraux G, Collette F. Functional imaging of cognition in Alzheimer's disease using positron emission tomography. Neuropsychologia 2008; 46: 1613–23.
Seeley WW, Carlin DA, Allman JM, Macedo MN, Bush C, Miller BL, et al. Early frontotemporal dementia targets neurons unique to apes and humans. Ann Neurol 2006; 60: 660–7.
Schroeter ML, Bücheler MM, Preul C, Scheid R, Schmiedel O, Guthke T, et al. Spontaneous slow hemodynamic oscillations are impaired in cerebral microangiopathy. J Cereb Blood Flow Metab 2005; 25: 1675–84.
Schroeter ML, Cutini S, Wahl M, Scheid R, von Cramon DY. Neurovascular coupling is impaired in cerebral microangiopathy - An event-related Stroop study. NeuroImage 2007a; 34: 26–34.
Schroeter ML, Ettrich B, Menz M, Zysset S. Traumatic brain injury affects the frontomedian cortex – An event-related fMRI study on evaluative judgments. Neuropsychologia 2010; 48: 185–93.
Schroeter ML, Ettrich B, Schwier C, Scheid R, Guthke T, von Cramon DY. Diffuse axonal injury due to traumatic brain injury alters inhibition of imitative response tendencies. Neuropsychologia 2007b; 45: 3149–56.
Schroeter ML, Neumann J. Combined imaging markers dissociate Alzheimer's disease and frontotemporal lobar degeneration – An ALE meta-analysis. Front Ag Neurosci 2011; 3: 1–6.
Schroeter ML, Raczka K, Neumann J, von Cramon DY. Towards a nosology for frontotemporal lobar degenerations - A meta-analysis involving 267 subjects. NeuroImage 2007c; 36: 497–510.

Schroeter ML, Raczka K, Neumann J, von Cramon DY. Neural networks in frontotemporal dementia - A meta-analysis. Neurobiol Aging 2008; 29: 418–26.

Schroeter ML, Stein T, Maslowski N, Neumann J. Neural correlates of Alzheimer's disease and mild cognitive impairment - A meta-analysis including 1351 patients. NeuroImage 2009; 47: 1196–206.

Schroeter ML, Vogt B, Frisch S, Becker G, Seese A, Barthel H, et al. Dissociating behavioral disorders in early dementia – An FDG-PET study. Psychiatry Res Neuroimaging 2011; 194: 235–44.

Schroeter ML, Zysset S, Kupka T, Kruggel F, von Cramon DY. Near-infrared spectroscopy can detect brain activity during a color-word matching Stroop task in an event-related design. Hum Brain Mapp 2002; 17: 61–71.

Schroeter ML, Zysset S, Kruggel F, von Cramon DY. Age-dependency of the hemodynamic response as measured by functional near-infrared spectroscopy. NeuroImage 2003; 19: 555–64.

Schroeter ML, Zysset S, Wahl M, von Cramon DY. Prefrontal activation due to Stroop interference increases during development - An event-related fNIRS study. NeuroImage 2004; 23: 1317–25.

Shallice T, Burgess P. Deficits in strategy application following frontal lobe damage in man. Brain 1991; 114: 727–41.

Strauss E, Sherman EM, Spreen O. A compendium of neuropsychological tests: administration, norms, and commentary. Oxford: University Press; 2006.

Stuss DT. Biological and psychological development of executive functions. Brain Cogn 1992; 20: 8–23.

Tabert MH, Manly JJ, Liu X, Pelton GH, Rosenblum S, Jacobs M, et al. Neuropsychological prediction of conversion to Alzheimer disease in patients with mild cognitive impairment. Arch Gen Psychiatry 2006; 63: 916–24.

Teipel SJ, Willoch F, Ishii K, Bürger K, Drzezga A, Engel R, et al. Resting state glucose utilization and the CERAD cognitive battery in patients with Alzheimer's disease. Neurobiol Aging 2006; 27: 681–90.

Thompson PM, Hayashi KM, de Zubicaray G, Janke AL, Rose SE, Semple J, et al. Dynamics of gray matter loss in Alzheimer's disease. J Neurosci 2003; 23: 994–1005.

van der Zee J, Sleegers K, van Broeckhoven C. The Alzheimer disease – frontotemporal lobar degeneration spectrum. Neurology 2008; 71: 1191–7.

Wilson B, Alderman N, Burgess PW, Emslie H, Evans JJ. Behavioral assessment of the dysexecutive syndrome. Bury St. Edmunds: Thames Valley Test company; 1996.

Winblad B, Palmer K, Kivipelto M, Jelic V, Fratiglioni L, Wahlund LO, et al. Mild cognitive impairment: beyond controversies, towards a consensus – Report of the international working group on mild cognitive impairment. J Intern Med 2004; 256: 240–6.

Wolfram H, Neumann J, Wieczorek V. Psychologische Leistungstests in der Neurologie und Psychiatrie [Psychological performance test for neurology and psychiatry]. Leipzig: Thieme; 1986.

Yakushev I, Landvogt C, Buchholz HG, Fellgiebel A, Hammers A, Scheurich A, et al. Choice of reference area in studies of Alzheimer's disease using positron emission tomography with fluorodeoxyglucose-F18. Psychiatry Res Neuroimaging 2008; 164: 143–53.