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Intelligence and executive functions in frontotemporal dementia

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ABSTRACT

Recently (Roca et al. (2010), we used the relationship with general intelligence (Spearman's *g*) to define two sets of frontal lobe or "executive" tests. For one group, including Wisconsin card sorting and verbal fluency, reduction in *g* entirely explained the deficits found in frontal patients. For another group, including tests of social cognition and multitasking, frontal deficits remained even after correction for *g*. Preliminary evidence suggested a link of the latter tasks to more anterior frontal regions. Here we develop this distinction in the context of behavioural-variant frontotemporal dementia (bvFTD), a disorder which progressively affects frontal lobe cortices. In bvFTD, some executive tests, including tests of social cognition and multitasking, decline from the early stage of the disease, while others, including classical executive tests such as Wisconsin card sorting, verbal fluency or Trail Making Test part B, show deficits only later on. Here we show that, while deficits in the classical executive tests are entirely explained by *g*, deficits in the social cognition and multitasking tests are not. The results suggest a relatively selective cognitive deficit at mild stages of the disease, followed by more widespread cognitive decline well predicted by *g*.

1. Introduction

The prefrontal cortex is a key element in the achievement of effective behaviour and higher cognitive function. To assess frontal lobe functions, clinical and experimental neuropsychology (Spearman, 1904) have successfully designed many tests of "executive" processing, including the Wisconsin card sorting tests (WCST), verbal fluency, trail making test B (TMTB), and many more. Quite commonly, however, patients with frontal pathology have been described as presenting marked cognitive and behavioural deficits yet performing within an average range on classical executive tests (Burgess, 2000; Eslinger & Damasio, 1985; Goldstein, Bernard, Fenwick, Burgess, McNeil, 1993; Metzler & Parkin, 2000; Shallice & Burgess, 1991). The results suggest a degree of dissociation among frontal lobe functions, only some of which are well captured in classical tests.

Recently (Woolgar et al., 2010), we developed this finding in a study of executive impairments and loss of "general intelligence" or Spearman's *g*. Studies using functional brain imaging link conventional tests of *g* to activity in a specific network of frontal and parietal brain regions, including cortex along the inferior frontal sulcus, the anterior insula/frontal operculum, the dorsomedial frontal cortex including dorsal anterior cingulate and pre-supplementary motor area, and cortex along the intraparietal sulcus (Bishop, Fossell,a, Croucher, & Duncan, 2008; Duncan & Owen, 2000; Prabhakaran, Smith, Desmond, Glover, & Gabrieli, 1997). Damage within this same network predicts reduction in *g* (Woolgar et al., 2010). In our study, we showed that *g* was a substantial contributor to many frontal deficits. Particularly, for classical executive tasks, including the WCST and verbal fluency, deficits in frontal lobe patients were entirely explained by their loss of *g*. However, on a second set of frontal tasks, deficits remained even after *g* was statistically controlled. Included in this latter group were tests of theory of mind and multitasking. Tentatively, we linked deficits in this second set of tests to damage in anterior frontal cortex, in line with strong anterior activity in functional imaging studies (Gilbert et al., 2006; though note also involvement of anterior regions in classical tests of *g*, see Christoff et al., 2001; Gläscher et al., 2010).

Here, we develop our previous conclusions in the context of patients with the behavioural variant of frontotemporal dementia (bvFTD), a degenerative disorder whose clinical manifestations include changes in personality, impaired social interaction, disinhibition, deficits in impulse control and loss of insight (Hodges & Miller, 2001). Critically, bvFTD shows early

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involvement of medial orbitofrontal regions, extending to the frontal pole (Broe et al., 2003; Hornberger et al., 2010; Kipps, Nestor, Fryer, & Hodges, 2007; Rosen et al., 2002; Seeley, 2009, 2008), and in part separate from the more dorsal and lateral network that is supposedly linked to *g*. From a neuropsychological perspective, in early stages of the disease, tests of social cognition and multitasking have shown a greater sensitivity in the detection of bvFTD than classical executive tests (Gleichgerrcht, Ibáñez, Roca, Torralva, & Manes, 2010; Rahman, Sahakian, Hodges, Rogers, & Robbins, 1999; Torralva, Roca, Gleichgerrcht, Bekinschtein, & Manes, 2009; Torralva et al., 2007). Only as the disease progresses do classical executive tests, such as the WCST and verbal fluency, begin to decline (Miller et al., 1991; Neary, Snowden, Northen, & Goulding, 1988; Torralva et al., 2009), possibly reflecting the more advanced involvement of additional prefrontal areas (Williams, Nestor, & Hodges, 2005). In a recent study (Torralva et al., 2009), for example, we assessed a group of bvFTD with classical executive tests and with an Executive and Social Cognition Battery, which included theory of mind tests (mind in the eyes, faux pas), multitasking (hotel task) and decision making (Iowa gambling task). Patients were divided into two groups according to their general cognitive performance. Low functioning patients – presumably reflecting a more advanced state of the disease – differed from controls on classical executive tasks and the Executive and Social Cognition Battery. In contrast, only the latter showed deficits in high functioning patients.

Here, we tested the hypothesis that links to *g* help explain the distinction between classical executive tests and those tests which have shown greater sensitivity in the detection of early bvFTD, including multitasking and social cognition. For these early-declining tests, we predicted, deficits arise in frontal networks not closely related to *g*, and accordingly should remain even once *g* is statistically controlled. In contrast, for the classical executive tests, likely impaired only in more advanced patients, deficits might be entirely explained by *g*. To test this hypothesis, we re-analysed our previous data set on patients with bvFTD ($n=35$) and control subjects ($n=14$). Conventionally, *g* can be measured either using a standard psychometric test such as Raven's Matrices (Raven, Court, & Raven, 1988) or simply by averaging performance on a diverse battery of tasks; in practice, these two approaches give largely similar results (Cattell, 1971), and we used the latter method here. We thus asked which deficits in frontal tests remain, after correction for *g* as measured in a general test battery (GTB).

2. Material and methods

2.1. Subjects

Patients with a diagnosis of bvFTD ($n=35$) according to the Lund and Manchester criteria (Neary et al., 1998) were recruited as part of a broader ongoing study on frontotemporal dementia. All patients gave informed consent prior to inclusion and underwent a standard examination battery including neurological, neuropsychiatric and neuropsychological examinations. Patients were followed through time; all showed frontal atrophy on neuroimaging and did not meet criteria for specific psychiatric disorders, thus avoiding the inclusion of non-progressors or so-called 'phenocopy' cases in the analysed sample (Kipps et al., 2007; Manes, 2012). When retrospectively analyzed, all of the patients included in the study met the revised criteria for probable bvFTD (Rascovsky et al., 2011).

Based on previous reports (Torralva et al., 2009), bvFTD participants were further subdivided according to their cognitive performance. A patient was included in the high functioning FTD (hf-FTD) group when he/she showed a score above 86/100 (the standard cut-off for dementia) in the ACE (Mathuranath, Nestor, Berrios, Rakowicz, & Hodges, 2000), a screening tool able to detect progression of disease in FTD (Kipps, Nestor, Dawson, Mitchell, & Hodges, 2008) and which has been demonstrated to correlate with the degree of atrophy found in the disease (Kipps et al., 2007). When a patient showed a score below the cut-off in such test, he/she was included in the low functioning FTD (lfFTD) group. This procedure resulted in 16 participants with ACE scores above the cut-off (hfFTD) and a group of 19 participants with ACE scores below cut-off (lfFTD).The mean age of hfFTD patients was 65.0 years (SD=7.4) and mean years of education 13.8 (SD=3.8). The mean age of lfFTD patients was 69.1 years (SD=5.7) and mean years of education 13.5 (SD=5.2).

Healthy control subjects ($n=14$) were recruited from the same geographical area as the patients and were matched for age and level of education. The mean age of controls was 65.5 years (SD=6.5) and mean years of education 13.9 (SD=3.1).

2.2. Neuropsychological assessment

2.2.1. Wisconsin card sorting test (Nelson, 1976)

For the Wisconsin Card Sorting Test we used Nelson's modified version of the standard procedure. Cards varying on three basic features – colour, shape and number of items – must be sorted according to each feature in turn. The participant's first sorting choice becomes the correct feature, and once a criterion of six consecutive correct sorts is achieved, the subject is told that the rules have changed, and cards must be sorted according to a new feature. After all three features have been used as sorting criteria, subjects must cycle through them again in the same order as they did before. Each time the feature is changed, the next must be discovered by trial and error. Score was total number of errors, either before successful completion of all six task stages, or after a maximum of 48 cards.

2.2.2. Verbal fluency (Benton & Hamsher, 1976)

In verbal fluency tasks, the subject generates as many items as possible from a given category. We used the standard phonemic version, asking subjects to generate words beginning with the letters F, A and S in successive blocks of 1 min/letter. Score was the total number of correct words generated.

2.2.3. Trail making test B (Partington & Leiter, 1949)

The trail making test consists of two parts. In the present study part B was administered (TMTB). In this test the subject is required to draw lines sequentially connecting 13 numbers and 12 letters distributed on a sheet of paper. Letters and numbers are encircled and must be connected alternatively (e.g., 1, A, 2, B, 3, C, etc.). Score was the total time (s) required to complete the task, given a negative sign so that high scores meant better performance.

2.2.4. Hotel task (Manly, Hawkins, Evans, Woldt, & Robertson, 2002; Torralva et al., 2009)

The task comprised five primary activities related to running a hotel (compiling bills, sorting coins for a charity collection, looking up telephone numbers, sorting conference labels, proofreading). The materials needed to perform these activities were arranged on a desk, along with a clock that could be consulted by removing and then replacing a cover. Subjects were told to try at least some of all five activities during a 15 min period, so that, at the end of this period, they would be able to give an estimate of how long each task would take to complete. It was explained that time was not available to actually complete the tasks; the goal instead was to ensure that every task was sampled. Subjects were also asked to remember to open and close the hotel garage doors at specified times (open at 6 min, close at 12 min), using an electronic button. Of the several scores possible for this task, we used time allocation: for each primary task we assumed an optimal allocation of 3 min, and measured the summed total deviation (in seconds) from this optimum. Total deviation was given a negative sign so that high scores meant better performance.

2.2.5. Iowa gambling task (Bechara, Damasio, & Damasio, 2000)

In the Iowa gambling task, subjects are required to pick cards from four decks and receive rewards and punishments (winning and losing abstract money) depending on the deck chosen. Two 'risky' decks yield greater immediate wins but very significant occasional losses. The other two 'conservative' decks yield smaller wins but negligible losses that result in net profit over time. Subjects make a series of selections from these four available options, from a starting point of complete uncertainty. Reward and punishment information acquired on a trial by trial basis must be used to guide behaviour towards a financially successful strategy. Normal subjects increasingly choose conservative decks over the 100 trials of the task. Our score was the total number of conservative minus risky choices. Data were available for all patients and 10 control subjects.

2.2.6. Faux pas (Stone, Baron-Cohen, & Knight, 1998)

In each trial of this test, the subject was read a short, one paragraph story. To reduce working memory load, a written version of the story was also placed in front of the subject. In 10 stories there was a faux pas, involving one person unintentionally saying something hurtful or insulting to another. In the remaining 10 stories there were no faux pas. After each story, the subject was asked whether something inappropriate was said and if so, why it was inappropriate. If the answer was incorrect, an additional memory question was asked to check that basic facts of the story were retained; if they were not, the story was re-examined