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Impaired acquisition rates of probabilistic associative learning in frontotemporal dementia is associated with fronto-striatal atrophy

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ABSTRACT

Frontotemporal dementia (FTD) is classically considered to be a neurodegenerative disease with cortical changes. Recent structural imaging findings, however, highlight that subcortical and in particular striatal regions are also affected in the FTD syndrome. The influence of striatal pathology on cognitive and behavioural changes in FTD is virtually unexplored. In the current study we employ the Weather Prediction Task (WPT), a probabilistic learning task which taps into striatal dysfunction, in a group of FTD patients. We also regressed the patients' behavioural performance with their grey matter atrophy via voxel-based morphometry (VBM) to identify the grey matter contributions to WPT performance in FTD. Based on previous studies we expected to see striatal and frontal atrophy to be involved in impaired probabilistic learning. Our behavioural results show that patients performed on a similar level to controls overall, however, there was a large variability of patient performance in the first 30 trials of the task, which are critical in the acquisition of the probabilistic learning rules. A VBM analysis covarying the performance for the first 30 trials across participants showed that atrophy in striatal but also frontal brain regions correlated with WPT performance in these trials. Closer inspection of performance across the first 30 trials revealed a subgroup of FTD patients that performed significantly poorly than the remaining patients and controls on the WPT, despite achieving the same level of probabilistic learning as the other groups in later trials. Additional VBM analyses revealed that the subgroup of FTD patients with poor early probabilistic learning in the first 30 trials showed greater striatal atrophy compared to the remaining FTD patients and controls. These findings suggest that the integrity of fronto-striatal regions is important for probabilistic learning in FTD, with striatal integrity in particular, determining the acquisition learning rate. These findings will therefore have implications for developing an easily administered version of the probabilistic learning task which can be used by clinicians to assess striatal functioning in neurodegenerative syndromes.

1. Introduction

Frontotemporal dementia (FTD) is a progressive neurodegenerative brain disorder characterised by predominant frontal and temporal neocortical atrophy. Three clinical variants of FTD are generally reported: behavioural variant (bvFTD), semantic dementia (SD) and progressive nonfluent aphasia (PNFA) (Hodges, 2007). Cognitive deficits specific to each variant are related to the pattern of underlying atrophy. bvFTD is characterised by behaviour and personality changes, such as reduced empathy, apathy, social inappropriateness and disinhibition (Piguet et al., 2011) and is associated with atrophy most pronounced in the ventromedial prefrontal cortex regions. The language variants of FTD present either with degradation of semantic knowledge (SD) associated with asymmetric anterior temporal lobe atrophy (generally left > right) or with language production difficulties (PNFA) observed in the context of left inferior frontal lobe and insular atrophy (Knibb et al., 2006; Hodges and Patterson, 2007). Importantly, however, recent evidence has shown atrophy to subcortical brain regions including the striatum (Broe et al., 2003; Chow et al., 2008; Looi et al., 2008; Garibotto et al., 2011), across FTD subtypes.

The cognitive and functional deficits in FTD arising from atrophy in these subcortical structures remain largely unknown. To our knowledge, the only study to date to examine functional deficits associated with

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striatal dysfunction in FTD employed a probabilistic learning task, the weather prediction task (WPT) (Weickert et al., 2011) and found that the behavioural variant of FTD is particular impaired on this task. The WPT has previously been shown to be a sensitive tool for identifying striatal dysfunction in patients with Parkinson's disease (PD), a neurodegenerative disorder which affects striatal brain regions (Knowlton et al., 1996a). The WPT requires participants to learn which of two outcomes (rain or shine) are predicted by different sets of geometric shapes. Outcomes are probabilistically assigned to each set. Participants must begin by guessing the outcome but over cumulative trials healthy individuals implicitly learn which outcome is most probable for each set. Such implicit learning tasks are thought to be dependent on striatal structures which are proposed to be involved in managing outcome expectancies (de Wit et al., 2007; Hare et al., 2008). Indeed, patients with predominant striatal damage as present in PD and Huntington's disease (HD) are impaired on the WPT task (Knowlton et al., 1996a, 1996b; Shohamy et al., 2004; Perretta et al., 2005). In contrast, patients with explicit memory loss following medial temporal lobe lesions, perform the WPT at the level of healthy control subjects (Knowlton et al., 1994).

Importantly, functional magnetic resonance imaging (fMRI) studies have highlighted that numerous frontal regions, in addition to striatal regions, are activated during successful performance on the WPT [for review see 17]. The importance of fronto-striatal white matter integrity for successful performance on a probabilistic reward learning task (Samanez-Larkin et al., 2012) provides further support that a fronto-striatal circuit may be crucial for probabilistic learning. In light of the evidence for fronto-striatal contributions to probabilistic association learning, it is unknown whether impaired performance on the WPT in FTD (Weickert et al., 2011) is more related to frontal or striatal abnormalities.

The current study aimed at establishing the brain correlates of WPT task performance in FTD. We hypothesised that atrophy specific to orbital frontal and striatal brain regions would be related to performance on the WPT task, corroborating previous patient studies and demonstrating the presence of striatal abnormalities in FTD patients.

2. Methods

2.1. Participants

Fifteen FTD patients participated in the study (bvFTD = 5; SD = 5; PNFA = 5). Patients met the current clinical diagnostic criteria for FTD (Gorno-Tempini et al., 2011; Rascovsky et al., 2011). Only patients with evidence of disease progression and brain atrophy on MRI were included to rule out behavioural-variant phenocopy cases (Kipps et al., 2010). Twelve healthy adults were selected from a healthy volunteer database at Neuroscience Research Australia or were spouses/carers of the FTD patients. Importantly, the healthy adults' WPT performance was matched to the patients. Exclusion criteria included other neurological conditions, a history of significant TBI, alcohol abuse, use of medications with CNS side effects and an Addenbrooke's Cognitive Examination — Revised (ACE-R) score of under 85. Additional exclusion criteria for MRI scanning included the presence of ferrous implants, pacemakers and claustrophobia. All participants underwent a battery of neuropsychological tests including the ACE-R as a general measure of cognitive impairment, the Rey Auditory Verbal Learning Test (RAVLT) as a measure of verbal learning and memory, and the Doors and People test as a measure of nonverbal memory function. All participants provided informed written consent prior to participation in this study. This study was approved by the University of New South Wales and the South Eastern Sydney and Illawarra Area Health Service Human Research Ethics Committees.

Table 1
Probability structure of probabilistic learning (Weather Prediction) test.

	Cue					
Cue pattern	1	2	3	4	P(cue combination)	P(outcome)
1	0	0	0	1	.133	.150
2	0	0	1	0	.087	.385
3	0	0	1	1	.080	.083
4	0	1	0	0	.087	.615
5	0	1	0	1	.067	.200
6	0	1	1	0	.040	.500
7	0	1	1	1	.047	.143
8	1	0	0	0	.133	.850
9	1	0	0	1	.067	.500
10	1	0	1	0	.067	.800
11	1	0	1	1	.033	.400
12	1	1	0	0	.080	.917
13	1	1	0	1	.033	.600
14	1	1	1	0	.047	.857

Note. For any given trial, 1 of the 14 possible cue pattern combinations displayed above appeared on the computer screen with a probability indicated as: P(cue combination). As shown above, the probability of the cue combinations to predict "sunshine" (outcome 1) was set at P(outcome). Conversely, the probability of the above cue combinations to predict "rain" (or outcome 2) was equal to 1 − P.

2.2. Probabilistic association learning test — WPT

Each participant was administered the probabilistic association learning Weather Prediction Test (Knowlton et al., 1994). The task consists of four cue cards containing patterns of different geometrical shapes presented on a laptop computer screen. In any given trial, one, two or three cue cards are displayed (see Fig. 1 for an example of a trial). Participants were instructed to make a decision to predict '*rain*' or '*shine*' based on the combination of the cue cards presented. They were told that they would need to guess at first but would gradually improve at determining which cue card combinations predict rain or shine based on feedback provided. The relation between cue cards and outcomes were determined on a probabilistic basis (see Table 1 for an example of a cue–outcome probability schedule). Stimulus presentations were randomised but each outcome (rain or shine) was limited to five consecutive occurrences. All stimuli were displayed on screen for 4.5 s with an inter-trial interval of .5 s. Participants responded with a left mouse button press by their right hand to choose either rain or shine. After each response the words 'correct' or 'incorrect' appeared on screen as feedback to the participant. Missed trials were not included in the analyses.

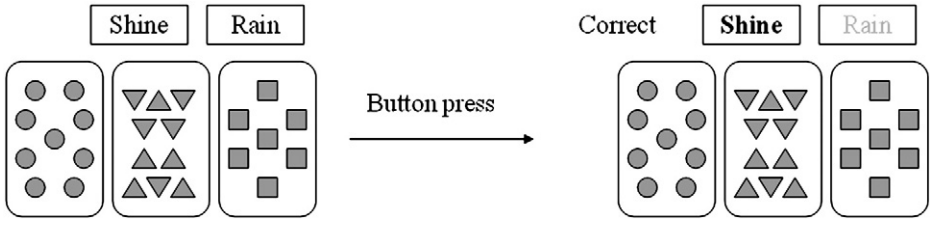

Fig. 1. Example of a probabilistic learning task trial.