Research report

Probabilistic association learning in frontotemporal dementia and schizophrenia

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A B S T R A C T

Introduction: Recent neuropsychological studies show substantial cognitive deficits in patients with frontotemporal dementia (FTD). Schizophrenia (SC) overlaps in terms of neurobehavioural symptoms with FTD. Probabilistic association learning, which is thought to assay fronto-striatal function, is well documented to elicit impairment in SC and has not been investigated in FTD to date; this study compared FTD, SC and a healthy comparison group on probabilistic association learning to determine the extent to which FTD patients were similar in performance to SC patients.

Methods: Twenty FTD patients, 24 SC patients and 26 healthy controls were assessed using the probabilistic association learning weather prediction test. FTD patients were also divided into behavioural and language variants for comparison to the healthy group.

Results: FTD patients were impaired during probabilistic association learning in comparison to healthy controls. There was no difference in performance between the FTD and SC groups. FTD behavioural variants performed significantly worse than the healthy comparison group, while FTD language variants did not differ from the healthy comparison group.

Conclusions: This study provides the first evidence for impaired probabilistic association learning in FTD which is of an equivalent degree to that seen in SC. These results support recent structural neuroimaging studies showing fronto-striatal abnormalities in FTD and suggest that fronto-striatal dysfunction may contribute to cognitive deficits in a significant proportion of people with FTD.

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1. Introduction

Frontotemporal dementia (FTD) is a young-onset dementia characterized by three clinical subtypes: a behavioural variant FTD, with deficits in inter-personal conduct, disinhibition, stereotypic behaviours, and loss of empathy and apathy; and two language variants: semantic dementia and progressive non-fluent aphasia who show progressive loss of word knowledge and language production deficits, respectively. Clinically, FTD patients are distinguished from Alzheimer

disease, in particular by their seemingly intact memory and thus, severe amnesia is currently seen as a diagnostic exclusion criterion for FTD (Neary et al., 1998). Nevertheless, there are conflicting findings on standard neuropsychological memory tasks with some studies showing memory deficits in FTD patients (Hornberger et al., 2010; Graham et al., 2005), while others have not (Lee et al., 2003; Glosser et al., 2002). These inconsistent findings have been explained by the admixture of patients with and without a neurodegenerative disease (Hornberger et al., 2010) but also by the nature of the neuropsychological memory tests employed since performance on standard memory tests may be affected by impairment in other cognitive domains. One aspect of cognitive processing, called probabilistic association learning, is a form of reinforcement learning that underlies decision processes. Presently little is known about probabilistic association learning in FTD.

One widely used probabilistic association learning test is called the weather prediction test (Knowlton et al., 1994). In brief, the task requires learning of probabilistic cue-outcome associations, putatively without conscious awareness. Studies in patients with damage to the caudate nucleus, as in Huntington’s disease, or connections from the substantia nigra, as in Parkinson’s disease, have shown a complete elimination of the acquisition rate over the early trials suggesting that acquisition of the probabilistic associations is dependent on the integrity of the caudate nucleus (Knowlton et al., 1996a, 1996b). Crucially, patients with frontal lobe damage, sparing basal ganglia structures, showed no deficit in the acquisition of the probabilistic associations (Knowlton et al., 1996a). However, functional neuroimaging studies of probabilistic association learning using the weather prediction test suggest a role for a broader fronto-striatal network, showing activity in both the dorsolateral prefrontal cortex and the striatum in healthy adults during acquisition of the probabilistic associations (Poldrack et al., 1999, 2001; Fera et al., 2005) and reduced caudate nucleus activity in Parkinson’s disease (Moody et al., 2004) and schizophrenia (SC) (Weickert et al., 2009).

The findings in SC are of relevance to FTD since recent work has highlighted consistencies among neuropsychiatric symptoms between FTD and SC (Velakoulis et al., 2009; Ziauddeen et al., 2011), notably the high rate of apathy in both disorders with loss of empathy and stereotypic patterns of behaviour. Moreover, deficits in Theory of Mind processing have been shown in both disorders (Lough et al., 2006; Kosmidis et al., 2008; Gregory et al., 2002; Kipps et al., 2009; Langdon et al., 2006). This may not be surprising since similar brain regions are known to be affected. For example, both FTD and SC patients show ventromedial frontal dysfunction (Seeley, 2008; Nakamura et al., 2008).

More interestingly for the current study, patients with SC display impaired performance on the probabilistic association learning weather prediction test (Weickert et al., 2002, 2010; Keri et al., 2005; Foerde et al., 2008; Horan et al., 2008). Fronto-striatal pathology in FTD has been highlighted in two recent studies. Looi et al. (2008) found atrophy of the putamen and caudate nuclei in a volumetric Magnetic Resonance Imaging (MRI) study of FTD patients. Similarly, Garibotto et al. (2011) found significant atrophy across all FTD subtypes in the striatum, especially in the caudate; however, the studies showing caudate abnormalities in FTD are few. Thus, both patients with SC and patients with FTD can show dysfunction of fronto-striatal circuitry.

Our aim was to compare the performance of patients with FTD and patients with SC on the probabilistic association learning weather prediction test. In light of the recent structural neuroimaging studies showing fronto-striatal abnormalities in FTD and given the primacy of prefrontal dysfunction in FTD, we hypothesized that FTD patients would be impaired relative to a healthy comparison group with respect to probabilistic association learning and the impairment would be to a similar degree as the impairment shown in patients with SC.

2. Methods

2.1. Participants

2.1.1. FTD patients

Twenty FTD patients (19 males and 1 female) were recruited from the FRONTIER Dementia Clinic database and participated in this study. Of the 20 FTD patients participating in this study, 9 were classified as behavioural variant FTD and 11 as the language variant (i.e., either semantic dementia or progressive non-fluent aphasia FTD). All FTD patients met consensus criteria for FTD (Neary et al., 1998) with insidious onset, decline in social behaviour and personal conduct, emotional blunting and loss of insight. Only patients with evidence of disease progression and brain atrophy on MRI were included to rule out the inclusion of behavioural phenocopy cases.

2.1.2. SC patients

Twenty-four people with SC, 13 males and 11 females, with a diagnosis of SC or schizoaffective disorder participated in this study. Patients who received concurrent axis I psychiatric diagnoses other than SC, had a history of current substance abuse, head injuries with concomitant loss of consciousness, seizures, central nervous system infection, diabetes, or hypertension, were excluded. All patients with SC or schizoaffective disorder were all receiving doses of antipsychotic medication at the time of testing with the majority receiving second-generation antipsychotics, such as clozapine, aripiprazole, and risperidone.

2.1.3. Healthy adults

Twenty-six healthy adults, 8 males and 18 females, age- and education-matched to FTD patients were selected from a healthy volunteer sample at Neuroscience Research Australia or were spouses/carers of the FTD patients.

2.1.4. Standard protocol approvals and patient consents

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 Illawarra Area Health Service Human Research Ethics Committees and was conducted in accordance with the Declaration of Helsinki.

2.2. Procedure

2.2.1. Probabilistic association learning test

Each volunteer was administered the weather prediction test. Stimuli were four cue cards containing patterns of different geometrical shapes presented on a laptop computer screen. In
any given trial, a stimulus consisted of one, two or three cue cards (see Fig. 1 for an example of a trial). Participants were told that they should make a decision to predict rain or shine based on the presence or absence of the cue cards. They were also told that they should guess at first, but gradually, based on feedback provided, they would improve at determining which cue card combinations predict rain or shine. The relationship between cue cards and outcome variables was predetermined on a probabilistic basis (see Table 1 for an example of a cue-outcome probability schedule), and presentations were randomized with the constraint that each outcome (rain or shine) was limited to five consecutive occurrences. All stimuli were displayed on screen for 4.5 sec with an intertrial interval of .5 sec. 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.

### 2.3. Analyses

Since only 18 out of the 20 FTD patients completed all 150 trials of the weather prediction test, all analyses were performed on the first 140 trials of the weather prediction test to utilize data from all 20 FTD patients. Analyses involved application of a series of repeated-measures Analysis of Variance (ANOVAs) on the cumulative mean percent correct scores in three blocks (trials: 1–50, 51–100, and 101–140) from the weather prediction test as dependent variables with diagnostic group (FTD, SC, controls) or FTD subtype (behavioural variant FTD, language variant FTD) and control group as grouping variables. Corrections for interdependencies among the cumulative percent correct dependent variables were calculated using Multivariate tests for repeated measures. Significant main effects and/or interactions with \( \alpha \) set at .05 were followed-up with post hoc Least Significant Difference (LSD) tests. Given the directional nature of our hypotheses, i.e., that FTD patients and SC patients will be impaired relative to a healthy comparison group, post hoc comparisons were based on one-tailed tests of significance with \( \alpha \) set at .05. The number of no responses was compared among groups using a separate one-way ANOVA. Also, given the difference in gender ratio between the FTD patients and healthy comparison group, an additional repeated-measures ANOVA was performed with percent correct in the three trial blocks as dependent variables and diagnostic group (FTD, SC, controls) and gender as grouping variables.

### 3. Results

#### 3.1. Demographics and neuropsychological data

As shown in Table 2 the three groups were well matched for years of education but as expected the SC group was significantly younger than the other two groups (\( p < .05 \)). As expected, performance on the Mini Mental State Examination (MMSE) and Addenbrookes’ Cognitive Examination-Revised (ACE-R) was significantly better in controls than in the FTD group (\( p < .01 \)). The significant difference in age between people with SC and the healthy comparison group was not further addressed for the following reasons: 1) the FTD group and not the SC group was the main focus of comparison with the healthy group and 2) the SC group would be expected to perform equal to or worse than the healthy older comparison group, whereas age would generally be thought to negatively influence performance relative to a younger group.

#### 3.2. Probabilistic association learning

Results of the main repeated-measures ANOVA contrasting the three diagnostic groups as grouping variables and cumulative percent correct at each trial block as dependent variables revealed no significant main effect of group, a significant main

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**Table 1** — Probability structure of probabilistic association learning (weather prediction) test.

<table>
<thead>
<tr>
<th>Cue pattern</th>
<th>Cue</th>
<th>p(Cue combination)</th>
<th>p(Outcome)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>0.133</td>
<td>0.150</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>0.087</td>
<td>0.385</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>0.080</td>
<td>0.803</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>0.087</td>
<td>0.615</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>0.067</td>
<td>0.200</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
<td>0.040</td>
<td>0.500</td>
</tr>
<tr>
<td>7</td>
<td>0</td>
<td>0.047</td>
<td>0.143</td>
</tr>
<tr>
<td>8</td>
<td>1</td>
<td>0.133</td>
<td>0.850</td>
</tr>
<tr>
<td>9</td>
<td>1</td>
<td>0.067</td>
<td>0.500</td>
</tr>
<tr>
<td>10</td>
<td>1</td>
<td>0.067</td>
<td>0.800</td>
</tr>
<tr>
<td>11</td>
<td>1</td>
<td>0.033</td>
<td>0.400</td>
</tr>
<tr>
<td>12</td>
<td>1</td>
<td>0.080</td>
<td>0.917</td>
</tr>
<tr>
<td>13</td>
<td>1</td>
<td>0.033</td>
<td>0.600</td>
</tr>
<tr>
<td>14</td>
<td>1</td>
<td>0.047</td>
<td>0.857</td>
</tr>
</tbody>
</table>

*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: \( p(\text{cue combination}) \). As shown above, the probability of the cue combinations to predict “sunshine” (outcome 1) was set at \( p(\text{outcome}) \). Conversely, the probability of the above cue combinations to predict “rain” (outcome 2) was equal to 1 – \( p(\text{outcome}) \).*
effect of trial block, \( F(2, 66) = 11.96, p < .001 \), and a significant trial block \( \times \) diagnostic group interaction, \( F(4, 132) = 3.59, p = .008 \) (see Fig. 2A). Post hoc LSD tests revealed a significant difference between FTD patients and the healthy comparison group at trial block 140, \( p = .025 \), and significant differences between SC patients and the healthy comparison group at trial blocks 100 and 140, \( p's = .04 \). There were no significant differences between FTD and SC patients. A separate one-way ANOVA on the number of no responses showed no significant difference in the number of no responses among FTD (mean = 9.4, Standard Error of the Mean (SEM) = 2.4), SC (mean = 10.2, SEM = 2.2), and healthy comparison (mean = 3.7, SEM = 2.1) groups. Also, the mean number of no responses for each group was low and did not exceed 7% of the total number of responses.

A further analysis with the FTD patients characterized as behavioural variant FTD (n = 9) and language variant (n = 11) relative to controls (see Fig. 2B) revealed a significant main effect of trial block, \( F(2, 42) = 17.63, p < .001 \), a significant trial block \( \times \) participant group interaction, \( F(4, 84) = 2.85, p = .03 \) and no other significant main effects or interactions. Post hoc LSD tests showed that the behavioural variant FTD performed significantly below the healthy adults at trial block 140, \( p = .05 \). Results of the ANOVA comparing the three trial blocks of weather prediction as the dependent variables and diagnostic group (FTD, SC, controls) and gender as grouping variables revealed no significant main effect of group, no significant main effect of gender, and no significant interaction among trial block, diagnosis, and gender.

### 4. Discussion

To our knowledge, this is the first study of probabilistic association learning in FTD. Relative to control participants, patients with FTD were impaired in the weather prediction test to an equivalent level found in SC. FTD patients differed significantly from the healthy comparison group during the latter trial block of probabilistic association learning and they did not differ significantly from the SC patients. When FTD patients were categorized on the basis of behavioural and language variant FTD patients, the behavioural variant FTD patients showed an impaired performance relative to the healthy comparison group during the latter trial block while the FTD language variants did not differ significantly from healthy comparison group. Thus, the significant difference between the healthy comparison group and FTD group in the combined behavioural and language FTD group appears to be driven mainly by the behavioural FTD patients, although in the final trial block the language variant FTD patients show a non-significant decline to near the level of the behavioural variant FTD patients.

Based on the Knowlton et al. (1996a, 1996b) interpretation, early trials (first 50 trials) would reflect striatal function and, therefore, striatal function would not appear to be affected in the language variant FTD patients since the first 50 trials do not differ significantly from controls. However, findings from healthy neuroimaging studies (Poldrack et al., 2001; Fera et al., 2003) suggest that striatal activity occurs during the latter trials of probabilistic association learning and thus, striatal function did appear to show a tendency towards impairment in the language variant FTD patients from the present study given the non-significant performance decline during the latter trials in language variant FTD patients. This finding also supports recent studies showing striatal abnormalities in

### Table 2 – Mean age, education, and cognitive assessments in FTD patients, people with SC, and healthy older adults.

<table>
<thead>
<tr>
<th></th>
<th>FTD</th>
<th>SC</th>
<th>Healthy older controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (M:F)</td>
<td>20 (19:1)</td>
<td>24 (13:11)</td>
<td>26 (8:18)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>62.6 (6.2)</td>
<td>37.2 (5.4)</td>
<td>67.4 (7.9)</td>
</tr>
<tr>
<td>Education (years)</td>
<td>12.9 (3.5)</td>
<td>12.8 (2.2)</td>
<td>11.8 (2.7)</td>
</tr>
<tr>
<td>MMSE (total score)</td>
<td>24.8 (4.5)</td>
<td>na</td>
<td>29.2 (94)</td>
</tr>
<tr>
<td>ACE-R (total score)</td>
<td>70.9 (15.1)</td>
<td>na</td>
<td>93.2 (3.5)</td>
</tr>
<tr>
<td>Duration of illness (yrs)</td>
<td>3.6 (2.0)</td>
<td>13.3 (5.4)</td>
<td>na</td>
</tr>
<tr>
<td>WAIS-III FSIQ estimate</td>
<td>na</td>
<td>97.0 (14.7)</td>
<td>na</td>
</tr>
</tbody>
</table>

Note: Standard deviation in parentheses. WAIS-III: Wechsler Adult Intelligence Scale-3rd Edition, Full Scale IQ estimate (FSIQ); na: not available/applicable.

Fig. 2 – A. Comparison of FTD, SC patients and healthy older comparison participants (OC) across 140 trials of probabilistic association learning. Whiskers denote standard error, * indicates significantly different from OC, \( p's = .04 \). B. Comparison of the FTD behavioural (behav) and language (lang) variants to healthy older adults (OC) across 140 trials of probabilistic association learning. Whiskers denote standard error, * indicates behavioural variant group significantly different from OC group, \( p = .05 \).
a percentage of language variant FTD patients (Garibotto et al., 2011; Looi et al., 2008).

SC patients have been shown previously to display an overall performance deficit on probabilistic association learning (Weickert et al., 2002; Keri et al., 2005; Horan et al., 2008) and two studies (Foerde et al., 2008; Weickert et al., 2010) have shown overall performance and acquisition rate deficits in SC. The probabilistic association learning deficit in SC has also been shown to be related to fronto-striatal dysfunction (Weickert et al., 2009). Interestingly, recent studies have also identified striatal atrophy in FTD (Looi et al., 2008; Garibotto et al., 2011; Chow et al., 2008), with primarily the behavioural variant FTD patients showing reduction of caudate and putamen volumes on MRI. Pathological studies have also shown involvement of basal ganglia structures in FTD from an early stage (Broe et al., 2003; Kril and Halliday, 2004). Such striatal abnormalities could explain the probabilistic learning deficits in the behavioural variant FTD group although more widespread cortical atrophy is also present particularly involving ventromedial and dorsolateral prefrontal cortex regions (Seeley, 2008; Whitwell et al., 2009). Importantantly, the seminal study using the weather prediction test by Knowlton et al. (1996a) showed that patients with lesions confined to the prefrontal cortex performed normally on this probabilistic association learning test, which suggests that the deficits seen in the behavioural variant FTD group may be more likely to be caused by the striatal pathology.

Conceptually, it is interesting that the behavioural variant FTD and SC patients performed so similarly on the weather prediction test. As previously noted, FTD patients have clear macroscopic atrophy in various cortical and subcortical regions, while SC only show minimal structural changes, if any and have more functional (e.g., neurotransmitter) deficits (Seeman et al., 1989; Laruelle et al., 1996; Pilowsky et al., 1994) although abnormal caudate nucleus volumes have also been reported (McClure et al., 2006; van Haren et al., 2007; Goldman et al., 2008), but these are typically related to antipsychotic dose. It is, therefore, striking that despite different pathology both groups show such similar profiles on the task. Given the overlap in behavioural features between SC and behavioural variant FTD it is surprising that so few comparative neuropsychological studies have been reported (Velakoulis et al., 2009; Ziauddeen et al., 2011). This is clearly fertile ground for further exploration.

In comparison to other dementias, the probabilistic association learning impairment found in FTD in the present study is in contrast to the lack of probabilistic association learning impairment demonstrated in patients with mild Alzheimer’s disease (Eldridge et al., 2002). These results are in accord with the known patterns of pathological involvement in FTD and Alzheimer’s Disease (AD). In AD there is major involvement of medial temporal lobe and associated limbic structures from an early stage while fronto-striatal structures are largely spared. By contrast in FTD, the basal ganglia are affected as discussed above.

There are clearly limitations to the present study. For example, the relatively small number of participants in each of the FTD subtypes limits interpretation. It would also be of considerable interest to combine behavioural and neuroimaging evaluation of FTD subgroups with larger numbers of participants. Also, the present study cannot distinguish between prefrontal and striatal dysfunction as being the contributing factor to impaired probabilistic association learning in FTD. Thus, further functional neuroimaging studies would also be interesting to determine the extent of frontal-striatal dysfunction in FTD during probabilistic association learning. As shown by Weickert et al. (2009) patients with SC classified as good learners can still display abnormal frontal-striatal activity that may be compensated by other brain regions (such as a more rostral region of the prefrontal cortex and/or the parahippocampal gyrus).

In conclusion, FTD patients showed deficits on probabilistic association learning to a similar extent to that shown by SC patients. This effect appeared to be primarily driven by the behavioural variant FTD patients since patients with language variants of FTD generally performed similarly to the healthy participants. These results showing poor probabilistic association learning in FTD is suggestive of subcortical pathology which could contribute to the clinical profile in behavioural variant FTD.

5. Role of the funding source

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6. Conflict of interest

All authors declare no conflict of interest that would inappropriately influence or be perceived to influence their work.

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References


