Strategic value-directed learning and memory in Alzheimer's disease and behavioural-variant frontotemporal dementia

Stephanie Wong[1,2,3,5], Muireann Irish[1,3,5,6], Greg Savage[1,2], John R. Hodges[1,3,4,6,7], Olivier Piguet[1,3,4,5,6] and Michael Hornberger[1,8,9]*

[1]ARC Centre of Excellence in Cognition and its Disorders, Sydney, Australia
[2]Department of Psychology, Macquarie University, Sydney, Australia
[3]Neuroscience Research Australia, Sydney, Australia
[4]School of Medical Sciences, University of New South Wales, Sydney, Australia
[5]School of Psychology, The University of Sydney, Sydney, Australia
[6]Brain & Mind Centre, The University of Sydney, Sydney, Australia
[7]Central Clinical School, Sydney Medical School, The University of Sydney, Sydney, Australia
[8]Norwich Medical School, University of East Anglia, Norwich, UK
[9]Dementia and Complexity in Later Life, NHS Norfolk and Suffolk Foundation Trust, UK

*Corresponding author:
Prof. Michael Hornberger
Norwich Medical School, University of East Anglia, NR4 7TJ, Norwich, UK
Tel: +44 1603 593540; Fax: +44 1603 593752; Email: m.hornberger@uea.ac.uk

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Abstract

In healthy adults, the ability to prioritize learning of highly valued information is supported by executive functions, and enhances subsequent memory retrieval for this information. In Alzheimer's disease (AD) and behavioural-variant frontotemporal dementia (bvFTD), marked deficits are evident in learning and memory, presenting in the context of executive dysfunction. It is unclear if these patients show a typical memory bias for higher valued stimuli. We administered a value-directed word-list learning task to AD (n=10) and bvFTD (n=21) patients and age-matched healthy controls (n=22). Each word was assigned a low, medium or high point value and participants were instructed to maximize the number of points earned across three learning trials. Participants' memory for the words was assessed on a delayed recall trial, followed by a recognition test for the words and corresponding point values. Relative to controls, both patient groups showed poorer overall learning, delayed recall and recognition. Despite these impairments, AD patients preferentially recalled high-value words on learning trials, and showed significant value-directed enhancement of recognition memory for the words and points. Conversely, bvFTD patients did not prioritize recall of high-value words during learning trials, and this reduced selectivity was related to inhibitory dysfunction. Nonetheless, bvFTD patients showed value-directed enhancement of recognition memory for the point values, suggesting a mismatch between memory of high-value information and the ability to apply this in a motivationally salient context. Our findings demonstrate that value-directed enhancement of memory may persist to some degree in patients with dementia, despite pronounced deficits in learning and memory.

Keywords: Alzheimer's disease; frontotemporal dementia; memory; executive function; reward

Introduction

Every day, we encounter enormous amounts of information, which vary in terms of relative value or importance. The ability to prioritise what we need to learn and remember for higher valued information is therefore critical for maximizing memory efficiency. Indeed, evidence suggests that reward value plays a key role in shaping episodic memory (Shohamy & Adcock, 2010). The cognitive mechanisms by which this effect is achieved, however, remain unclear.

Encoding selectivity has been examined in healthy adults using the value-directed remembering (VDR) paradigm (Castel, Benjamin, Craik, & Watkins, 2002), where participants are presented with lists of words, which are each assigned a point value to signify its relative importance. A consistent finding in studies of both young and older healthy adults is that the probability of immediate (short-term) word recall increases with point value (Castel et al., 2002; Castel, Farb, & Craik, 2007). Importantly, age-related differences in recall are observed for words with lower values but not those with higher values, indicating that the ability to prioritise memory for highly valued information persists with healthy aging, despite declines in memory for less valued information (Castel et al., 2002). Furthermore, higher selectivity in encoding is associated with greater working memory capacity (Castel, Balota, & McCabe, 2009; Hayes, Kelly, & Smith, 2013) and enhances subsequent recognition memory for the words and associated point values, such that higher valued words are more accurately retrieved (Castel et al., 2007; McDonough, Bui, Friedman, & Castel, 2015).

Value-directed remembering therefore has interventional potential in neurodegenerative syndromes in which marked episodic memory deficits are present. Behavioural-variant frontotemporal dementia (bvFTD) and Alzheimer's disease (AD) are two such syndromes in which episodic memory impairments are well-established, but have been proposed to be driven by different neurocognitive mechanisms. Owing to the predominantly prefrontal burden of neuropathology and prominent executive dysfunction in bvFTD (Kipps, Hodges, Fryer, & Nestor, 2009; Kramer et al., 2005), it has been suggested that deficits in strategic encoding and retrieval mechanisms underlie episodic memory impairment in these patients (Pasquier, Grymonprez, & Lebert, 2001; Wicklund, Johnson, Rademaker, Weitner, & Weintraub, 2006). However, both prefrontal and medial temporal lobe regions have been implicated in episodic memory dysfunction in bvFTD (Irish, Piguet, Hodges, & Hornberger, 2014; Pennington, Hodges, & Hornberger, 2011). Conversely, episodic memory deficits in AD are considered to reflect deficits in memory encoding, storage and consolidation (Golby et al., 2005; Lekeu et al., 2010), attributable to atrophy predominantly in the medial temporal lobes and posteromedial cortices (Irish et al., 2016; Ranganath & Ritchey, 2012). Concomitant deficits in executive function, however, are also commonly reported in AD (Swanberg, Tractenberg, Mohs, Thal, & Cummings, 2004), particularly with progression of the disease (Ramanan et al., 2016). Nevertheless, the degree to which executive deficits

differentially contribute to episodic memory dysfunction in bvFTD and AD remains largely underexplored.

To our knowledge, only one study has investigated value-directed memory selectivity in AD (Castel et al., 2009). Using the VDR paradigm, Castel et al. (2009) found that AD patients showed better immediate recall of high-value compared to low-value words. On the other hand, value-directed memory selectivity has not been investigated in bvFTD. Importantly, AD and bvFTD patients show similar impairments in working memory and cognitive flexibility (Giovagnoli, Erbetta, Reati, & Bugiani, 2008). In contrast, bvFTD patients show disproportionate impairments in inhibitory control and value-based decision-making, which are associated with degenerative changes in the ventromedial prefrontal cortex and striatum (Hornberger et al., 2010; Kloeters, Bertoux, O'Callaghan, Hodges, & Hornberger, 2013; O'Callaghan, Naismith, Hodges, Lewis, & Hornberger, 2013). Nonetheless, it remains to be explored whether deficits in inhibitory control and value-based processing can impact on learning and memory. Of primary interest is whether value-directed memory selectivity is comparably affected across AD and bvFTD, and the underlying cognitive mechanisms driving any such deficits.

In addition to examining how memory selectivity is affected in AD and bvFTD, we were also interested in investigating the impact of value-directed encoding on subsequent memory retrieval. While healthy older adults show enhanced memory for rewarding stimuli (Castel, Balota, & McCabe, 2008; Spaniol, Schain, & Bowen, 2014), it is unclear whether reward value is sufficient to ameliorate memory impairments in neurodegenerative conditions. Whether a value-directed memory enhancement effect persists in patients with dementia is of clinical relevance, given the potential therapeutic implications in supporting memory for information that holds greater relative value.

The first aim of this study was to assess strategic value-directed encoding in AD and bvFTD using a simplified version of the VDR paradigm, where the same word-list is presented over three immediate recall learning trials, followed by a delayed recall trial and recognition test. Considering the widespread executive dysfunction and deficits in value-based decision making in bvFTD, we hypothesized that value would have no effect on immediate recall in bvFTD. In contrast, AD patients may learn to prioritise recall of higher valued words over repeated trials, in keeping with previous reports of greater recall of high-value versus low-

value words in this patient group. Secondly, we aimed to examine the relationship between encoding selectivity and profiles of executive dysfunction, to investigate whether deficits in working memory, cognitive flexibility and inhibition differentially associate with selectivity in AD and bvFTD. The final aim of this study was to explore whether reward value would enhance memory for the words and associated point values following a time delay. We hypothesised that value-directed enhancement of memory would be evident in AD, but attenuated in bvFTD patients, in-line with their expected performance on the preceding immediate recall trials.

Material and methods

Participants

Thirty-one dementia patients (bvFTD=21; AD=10) and 22 age-matched healthy controls were recruited. All bvFTD patients fulfilled clinical diagnostic criteria for probable bvFTD (Rascovsky et al., 2011), with insidious onset, progressive decline in social behaviour and personal conduct, apathy, emotional blunting and loss of insight and presence of frontal atrophy on brain imaging. All AD patients met clinical diagnostic criteria for probable AD (McKhann et al., 2011), with worsening episodic memory impairment in the context of preserved personality and behaviour and evidence of medial temporal lobe atrophy on imaging. Disease duration was estimated as the number of years elapsed since the reported onset of symptoms. The Frontotemporal Dementia Rating Scale (FRS; Mioshi, Hsieh, Savage, Hornberger, & Hodges, 2010) and Clinical Dementia Rating Scale (CDR; Morris, 1997) were used to determine disease severity in bvFTD and AD patients. All participants underwent general cognitive screening using the Addenbrooke's Cognitive Examination-III (ACE-III; Hsieh, Schubert, Hoon, Mioshi, & Hodges, 2013) to determine their overall level of cognitive functioning. Age-matched healthy controls were recruited from a research volunteer panel and scored >88 on the ACE-III (Hsieh et al., 2013).

Exclusion criteria for all participants included current or prior history of mental illness, significant head injury, movement disorders, cerebrovascular disease (stroke, transient ischaemic attacks), alcohol or other drug abuse and limited English proficiency.

Ethics statement

All participants provided written informed consent and this study was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained from local Human Research Ethics Committees.

Assessment of executive function and verbal episodic memory

Assessment of executive function included measures of working memory (Digit Span Backward (DSB); total score; Wechsler, 1997), cognitive flexibility (Trail Making Test; B-A time; Reitan & Wolfson, 1985) and verbal inhibition (Hayling Sentence Completion Test; AB error score; Burgess & Shallice, 1997). Further details of the executive function tests are detailed in Appendix A.

All participants underwent comprehensive neuropsychological assessment of verbal episodic memory in terms of immediate recall, delayed recall, and delayed recognition using the Rey Auditory Verbal Learning Test (RAVLT; Rey, 1941). Further details are provided in Appendix A.

Value-directed memory task

The value-directed memory (VDM) task was adapted from previous studies (Castel et al., 2008; 2009). The current version assessed learning, recall and recognition of a list of 12 words, where each word was assigned a value of 1, 5 or 10 points.

Stimuli and materials

The stimuli consisted of two lists of 12 words. Words from List 1 were presented during learning, while those in List 2 were presented as novel lures during the recognition memory test. Within List 1, 4 words were assigned to each of the low (1 point), medium (5 points) and high (10 points) value conditions. All words were concrete nouns containing either 4 or 5 letters. Words assigned to each condition were matched in terms of word frequency, familiarity, concreteness and imageability, determined using the MRC Psycholinguistic Database (http://www.psych.rl.ac.uk). Lists and words assigned per task phase and condition were counterbalanced across participants.

The VDM task was programmed using E-Prime 2.0 software (Psychology Software Tools, Pittsburgh, PA), and testing was conducted on a laptop with a 14-inch LED-backlit display. Participants responded verbally on the immediate recall learning trials, delayed recall trial and recognition tests.

Procedure

Following presentation of instructions, participants were presented with examples of the word and point stimuli. This included presentation of 3 words (worth 1, 5 and 10 points), followed by an immediate recall trial. After participants recalled the example words, feedback was provided regarding the total number of points earned and how this number was calculated. Participants were told that the aim of the task was to gain as many points as possible. Participants' understanding of the task instructions was checked before commencing the experimental task. Procedures for the learning and test phases are illustrated in Figure 1.

Learning phase

On each learning trial, participants viewed a list of 12 words, displayed one at a time on the computer screen. The order of presentation was randomised, with no more than 2 words from the same condition appearing consecutively. Each word was displayed for 2000 ms before the associated point value appeared below the word for an additional 2000 ms. Following presentation of the word list, participants were asked to recall as many words as possible from the list. Participants then received feedback regarding their total point score and were encouraged to beat their previous score on each upcoming trial. This procedure was repeated for trials 2 and 3 of the learning phase. To limit list-order effects, word-list presentation was randomised on each trial.

Following the learning phase, participants were asked to describe their encoding strategy throughout the 3 trials of the learning phase. Based on their responses, strategies were categorised as Type 1) 'focusing more on high-value words' or 2) 'ignoring value'.

Test phase

Delayed recall

A surprise recall test was administered following a 20-minute delay, during which participants completed a reading comprehension task for a separate study. On the delayed recall test, participants were asked to recall as many words as possible from the learning phase. Participants did not have a time limit for recall. No feedback was provided regarding the number of points earned.

Word and points recognition

Immediately after the delayed recall trial, recognition memory for the words and associated point values was assessed. The recognition phase consisted of 24 trials, where all 12 of the words from the learning phase were individually displayed, intermixed with the 12 novel lure words. On each trial, participants first made a word recognition decision by judging whether they had seen the word during the learning phase (yes/no) or whether they didn't know ("don't know"). The prompt "Yes | No | Don't know" was written below the word. Following each "yes" response, participants made a point recognition decision by responding whether that word had been worth 1, 5 or 10 points. The prompt "1 | 5 | 10 | Don't know" was displayed below the word. The point recognition question was not asked following "no" or "don't know" responses on the word recognition question. The "don't know" response option was offered in order to reduce potential contamination of guessing, in accordance with previously reported procedures (Leshikar & Duarte, 2013; Wong et al., 2017). Recognition trials were self-paced and presented in a random order. No feedback was provided regarding response accuracy.

Outcome measures

Learning phase

Outcome measures from the 3 immediate recall learning trials were the number of words recalled in each value condition. Participants' self-reported encoding strategies were also included as a categorical outcome measure. Finally, to examine value-directed strategic encoding ability, a selectivity index was calculated using the following equation:

As previously described (Ariel & Castel, 2013; Cohen, Rissman, Suthana, Castel, & Knowlton, 2016), the SI is a measure of a participant's point score, after taking into account the ideal point score and the chance point scores, which is weighted by the number of words recalled. The ideal point score is the maximum number of points that can be earned for recalling n number of words (e.g. the ideal point score for recalling 4 words is 10 + 10 + 10 + 10 = 40). The chance score represents the average points earned, and is calculated as the mean point value of the 12 words on each learning trial (i.e. 5.33). In line with previously reported procedures (Cohen et al., 2016), the weighting procedure was employed to account for low overall word recall performance in AD and bvFTD patients. SI scores range from 0 to 1, with values close to 1 indicating greater selectivity for high-value words. The trial 3 SI

score was included in our analyses as a measure of participants' ability to develop value-directed strategic encoding by the end of the learning phase.

Test phase

Delayed recall

The number of words recalled on each value condition was included as the outcome measure on the delayed recall trial.

Word recognition

Word recognition responses were classified as 'studied word hit' (correct recognition), 'studied word miss' (incorrect rejection) and 'studied DK (don't know)' for words previously seen during the learning phase; and 'unstudied word hit' (correct rejection), 'unstudied word miss' (false alarm) and 'unstudied DK' for novel words presented in the test phase only. To correct for false alarms per condition, corrected word recognition was calculated by subtracting the percentage of false alarms (number of false alarms / 12 × 100) from the percentage of correct recognition responses in each condition (e.g. number of correct recognition $_{\text{low-value}}$ / 4 × 100).

Points recognition

Points recognition responses were classified as 'points-recollected' (i.e. points-correct) or 'points-unrecollected' (i.e. 'points-incorrect' or 'points-don't know'). Given that the points recognition question was not asked following "no" or "don't know" word recognition responses, points recognition for such words were classified as 'points-unrecollected'. As the points recognition question was asked following each "yes" response to the word recognition question, regardless of whether the response was classified as 'correct recognition' or 'false alarm', the point value subsequently ascribed to each 'false alarm' was not analysed. Following previously reported procedures (Rosa, Deason, Budson, & Gutchess, 2014), points recognition accuracy was calculated by taking the percentage of points-correct responses out of the total number of words in each condition (e.g. percentage points-correct $_{\text{low-value}}$ = (points-correct $_{\text{low-value}}$ / 4) × 100).

Statistical analyses

Data were analysed using SPSS 20.0 (SPSS Inc., Chicago, ILL., USA). Normally distributed variables, as determined by Shapiro-Wilks tests, were compared across groups using ANOVAs followed by Tukey post hoc tests. Data that were not normally distributed were analysed using Kruskal-Wallis tests followed by post hoc pairwise comparisons, using Dunn's (1964) procedure with a Bonferroni correction for multiple comparisons. A chi-squared test was used to compare sex distribution across groups.

For each recall trial (Trials 1–3 immediate recall, delayed recall), a group (3) × condition (3) repeated measures ANOVAs was conducted to contrast the number of words recalled per condition across groups. Similarly, group (3) × condition (3) repeated measures ANOVAs were conducted to contrast corrected word and points recognition across conditions and groups. Post hoc simple-effects tests were conducted to examine differences between conditions within each participant group. All pairwise comparisons of the main effects and simple effects were adjusted for multiple comparisons using the Sidak method.

Due to the small numbers of participants reporting certain strategy types, Fisher's exact test was used to compare the distribution of participants' self-reported encoding strategies across groups. Independent samples t-tests were used to determine whether Trial 3 SI scores, delayed recall, word recognition or points recognition differed according to self-reported encoding strategy use.

Within each group, Spearman rank correlations were used to examine relationships between encoding selectivity on Trial 3 of the VDM task (SI scores) and background neuropsychological measures of executive function (DSB total, TMT B – A time and Hayling AB error score) and verbal episodic memory encoding (RAVLT learning trial 5 recall). A one-tailed significance level, corrected for multiple comparisons at of $p<.01$ was applied for all correlational analyses.

Results

Demographics

Demographics and clinical characteristics are detailed in Table 1. Shapiro-Wilk tests indicated that age, total years of education, disease severity (CDR SoB) and functional impairment (FRS) data were normally distributed, whereas measures of disease duration and

general cognition (ACE-III) showed non-normal distributions. Participant groups were matched for age (p=.091) and sex distribution (p=.363). An overall group difference was evident for total years of education (p=.007), with controls being more educated than bvFTD patients (p=.005). Total years of education did not differ between the two patient groups (p=.558) or between AD patients and controls (p=.264). Importantly, the patient groups were matched for disease duration (p=.751) and disease severity (CDR SoB; p=.991). The bvFTD patients showed a trend towards higher levels of functional impairment relative to AD patients (FRS; p=.066). While both patient groups were significantly impaired relative to controls (all p values <.001) on the ACE-III cognitive screening measure, performance was comparable for bvFTD and AD patients (p=.353).

Assessment of executive function and verbal episodic memory

Background executive function and verbal episodic memory variables showing normal distributions included RAVLT learning trials 2 and 3, with the remaining variables showing non-normal distributions. Patient groups displayed characteristic profiles of executive dysfunction relative to controls on tests of working memory (DSB; p values <.001), cognitive flexibility (TMT B – A time; p values <.001) and verbal inhibition (Hayling AB error score; p values <.014). No significant differences were evident between AD and bvFTD patients on any of the executive measures (p values >.47). Encoding, delayed recall and corrected recognition performance on the RAVLT are detailed in Table 1. Verbal episodic memory was significantly compromised in both patient groups relative to controls across all learning trials (RAVLT learning trials 1–5; p values <.001), delayed recall (RAVLT 30-minute recall; p values <.001) and corrected recognition (RAVLT corrected recognition; p values <.001). AD and bvFTD patients did not differ on any measures of verbal episodic memory performance (p values >.110).

Value-directed memory task results

Learning phase

Words recalled per condition

The number of low-, medium- and high-value words recalled per learning trial are illustrated in Figure 2A–C. Separate group × condition repeated measures ANOVAs were conducted for each learning trial. The group × condition interaction was significant on trials 1, 2 and 3 (Trial 1: $F_{4,100}$=4.271, p=.003; Trial 2: $F_{4,100}$=3.901, p=.006; Trial 3: $F_{4,100}$=3.819, p=.006),

indicating that differences in the recall of low-, medium- and high-value words varied across groups. Post hoc simple effects tests revealed that controls recalled significantly fewer low-value compared to medium-value (p values <.012) and high-value (p values <.001) across trials 1, 2 and 3. Furthermore, while controls recalled similar numbers of medium- and high-value words on Trials 1 and 3 (p values >.281), they recalled significantly more high-value compared to medium-value words on Trial 2 (p=.025). In AD patients, recall of low-, medium- and high-value words did not differ on trials 1 or 2. On trial 3 however, AD patients recalled significantly more high-value compared to low-value words (p=.023) and showed a trend towards recalling more medium-value compared to low-value words (p=.06). In contrast, bvFTD patients did not show any value-directed prioritisation of word recall, with similar numbers of low-, medium- and high-value words recalled across the 3 learning trials (p values >.159).

In addition, analyses for Trial 1, 2 and 3 each revealed significant main effects of group (Trial 1: $F_{2,50}$=26.091, p<.001; Trial 2: $F_{2,50}$=36.801, p<.001; Trial 3: $F_{2,50}$=43.393, p<.001), with controls outperforming AD (p<.001) and bvFTD (p<.001) patients. No significant group differences were evident when comparing AD and bvFTD patients on each of the learning trials (Trial 1: p=.399; Trial 2: p=.109; Trial 3: p=.091). Significant condition effects were also observed on each learning trial (Trial 1: $F_{2,100}$=15.214, p<.001; Trial 2: $F_{2,100}$=6.241, p=.003; Trial 3: $F_{2,100}$=14.452, p<.001), reflecting the greater number of high-value versus low-value words recalled (p values <.004). Across all groups, more medium-value versus low-value words were recalled on Trials 1 and 3 (p<.001) but not Trial 2 (p=.107). Recall of medium- and high-value words did not differ on any of the learning trials, averaged across all groups (p values >.311). Overall, results from the immediate recall learning trials indicate that controls showed a robust value-directed enhancement effect on encoding across all 3 trials. Whereas AD patients were able develop a value-directed encoding strategy by the 3rd learning trial, bvFTD patients did not appear to prioritise recall of higher value words across trials.

Self-reported encoding strategy

Participants' self-reported encoding strategies were categorised as 1) focusing more on high-value words or; 2) did not focus on the value of the words. Results from Fisher's exact test revealed that the distribution of encoding strategies was significantly different across groups (p=.004). The most commonly reported strategy in controls (86.4%) and AD patients (60%)

was ‘focusing more on high-value words’. In contrast, responses from bvFTD patients indicated that they had not implemented any specific encoding strategy, and when prompted with the two strategy types, the majority (61.9%) reported that they ‘did not focus on the value of the words’.

Within AD patients, those who reported ‘focusing more on high-value words’ had significantly higher Trial 3 SI scores compared to those who ‘did not focus on the value of the words’ (t_8=3.375, p=.01). In contrast, Trial 3 SI scores did not differ according to self-reported encoding strategy use in bvFTD patients (t_{19}=0.432, p=.671). In other words, self-reported encoding selectivity did not appear to be related to actual encoding selectivity in bvFTD. Performance on subsequent word recall, word recognition and points recognition measures did not differ between these strategy-based subgroups in AD or bvFTD (p values >.05).

Selectivity index from immediate recall learning Trial 3

SI scores from the 3rd immediate recall learning trial provide a measure of value-directed strategic encoding ability at the end of the learning phase. Mean Trial 3 SI scores in both AD (M=.81; SD=.13, p=.014) and bvFTD (M=.74, SD=.23, p<.001) were significantly lower than controls (M=.94, SD=.12), though the two patient groups did not differ (p=1.0). Analyses of SI scores across all 3 immediate recall learning trials are included in Appendix C.

Relationships between Trial 3 selectivity index, executive function and episodic memory

The ability to prioritise recall of high-value words by Trial 3 of the VDM task learning phase differentially associated with executive function across patient groups (see Table 2). In bvFTD, higher selectivity on Trial 3 was significantly associated with better performance on measures of verbal inhibition (r=–.560, p=.01). Weak associations between Trial 3 selectivity and working memory (DSB: r=.384, p=.044) and cognitive flexibility (r=–.416, p=.048) were also identified, but these did not reach significance after correcting for multiple comparisons. In contrast, no significant associations were identified between Trial 3 SI scores and performance on tests of executive function in AD patients (all p values >.119) or controls (all p values >.267). Furthermore, selectivity on Trial 3 of the VDM task was not significantly associated with verbal episodic memory encoding performance on the final learning trial of the RAVLT in any of the participant groups (p values >.104). Altogether, results from our

correlational analyses indicate a specific association between value-directed strategic encoding and inhibitory dysfunction in bvFTD patients only. Conversely, correlational analyses within each group revealed that encoding selectivity on the final learning trial is not related to verbal episodic learning capacity, as indexed on the final learning trial of a separate word-list learning task (RAVLT Trial 5 total words recalled; all p values>.103)

Test phase

Delayed recall

The number of low-, medium- and high-value words recalled on the delayed recall trial are shown in Figure 2D. Results from a repeated measures ANOVA revealed a trend towards a significant group × condition interaction ($F_{4,100}$=2.456, p=.051), suggesting that the condition effect varied across groups. Post hoc simple effects tests indicated that controls recalled significantly more high- and medium-value compared to low-value words (p values <.006), whereas recall of medium- and high-value words did not differ significantly (p=.959). In contrast, no such value-directed enhancement effect was observed in the delayed recall of low-, medium- and high-value words in AD (p values >.688) or bvFTD (p values <.199) patients. There was also a significant main effect of group ($F_{2,50}$=30.172, p<.001), where controls outperformed both AD (p<.001) and bvFTD (p<.001) patients. The overall effect of condition was not significant ($F_{2,100}$=2.706, p=.072). Overall, our results indicate that a value-directed enhancement effect on delayed recall memory was evident in controls but not AD or bvFTD patients. Analyses of the total number of words recalled and points earned on the delayed recall trial, regardless of condition, are included in Appendix B.

Word recognition

Figure 3A depicts corrected word recognition accuracy (hits – false alarms) for each condition across AD, bvFTD and controls. A group (3) by condition (3) repeated measures ANOVA revealed a significant group effect for corrected word recognition accuracy ($F_{2,50}$=12.668, p<.001). This group effect was driven by significantly lower corrected word recognition accuracy in both AD (p<.001) and bvFTD (p<.001) patients relative to controls, though the two patient groups did not differ (p=.841). The main effect of condition was significant ($F_{2,100}$=7.773, p=.001), with greater corrected recognition accuracy in the high-value compared to low-value condition (p=.001), a trend towards greater accuracy in the medium-value compared to low-value condition (p=.062) and no significant difference

between the medium- and high-value conditions (p=.449). There was no significant interaction between group and condition ($F_{4,100}$=0.446, p=.775). Post hoc simple effects tests revealed that within the control and bvFTD groups, corrected word recognition accuracy did not differ between conditions (controls: low- vs. medium-value p=.377; low- vs. high-value p=.174; medium- vs. high-value p=.993; bvFTD: low- vs. medium-value p=.635, low- vs. high-value p=.094, medium- vs. high-value p=.707). In contrast, AD patients showed significantly greater word recognition hits in the high-value compared to low-value condition (p=.02), with no significant difference between the medium- and low-value conditions (p=.328) or the high- and medium-value conditions(p=.651). Thus, overall corrected word recognition accuracy was similar across conditions in controls and bvFTD patients, whereas AD patients showed significant value-directed enhancement of memory for high-value compared to low-value words. Analyses of uncorrected word recognition hits are included in Appendix D.

Points recognition

Figure 3B depicts points recognition accuracy for each condition across AD, bvFTD and controls. An overall group effect on points recognition accuracy was evident ($F_{2,50}$=14.96, p=<.001), driven by significantly lower accuracy in both AD (p<.001) and bvFTD (p<.001) compared to controls. There was also a significant main effect of condition ($F_{2,100}$=11.317, p<.001), where high-value words were recognised more accurately than low- (p<.001) and medium-value (p=.002) words. No significant difference was observed between low- and medium-value words (p=.613). The interaction between group and condition was not significant ($F_{4,100}$=1.438, p=.227). However, post hoc simple effects tests revealed that within controls, points recognition was significantly higher in the high-value compared to medium-value conditions (p=.012), with no significant differences between low- and medium-value (p=.377) or low- and high-value (p=.363) conditions. Conversely, only the difference between low- and high-value conditions was significant in AD (p=.03) and bvFTD (p=.016) patients. As such, both patient groups showed significant value-directed enhancement of memory for the points associated with high-value compared to low-value words, whereas this effect was most pronounced between high- and medium-value words in controls. Additional analyses exploring potential response biases on points recognition are included in Appendix E.

Discussion

This is the first study to investigate preferential learning and retention of novel information that varies according to allocated value in two neurodegenerative syndromes. Our results in AD suggest that value-directed learning may support subsequent recognition memory for high-value information, despite showing no benefit for delayed free recall performance. In contrast, bvFTD patients did not preferentially recall high-value information during the learning phase, and this appeared to be associated with inhibitory dysfunction. Here, we discuss the implications of our findings in terms of in the underlying cognitive mechanisms that contribute to value-directed learning and memory in these patient groups.

Value-directed learning

In AD, word-list learning was influenced by the value assigned to each word. With the opportunity to strategically encode high-value words across three immediate recall learning trials, AD patients learned to preferentially recall more high-value relative to low-value words. This is consistent with previous findings in AD (Castel et al., 2009). Importantly, when asked about their encoding strategy, the majority of AD patients reported having focused more on high-value words. Furthermore, those who reported prioritising encoding of high-value words showed higher selectivity on the final learning trial. Our findings in AD therefore demonstrate a relatively preserved capacity for value-directed learning over repeated trials, despite an overall reduction in the total number of words recalled.

In contrast, no clear evidence of preferential learning according to value was observed in bvFTD patients, where the number of low-, medium- and high-value words did not differ across trials. While this appeared to be corroborated by the encoding strategies reported by bvFTD patients—the majority of whom reported ignoring the value of the words—it is important to note that there was no clear relationship between self-reported selectivity and actual selectivity as indexed on the final learning trial. This mismatch may be related to loss of insight, which is frequently reported in bvFTD (Banks & Weintraub, 2009; Hornberger et al., 2014). Nonetheless, our novel finding of impaired strategic value-directed learning in bvFTD align with previous findings which suggest that strategic encoding deficits impact on episodic memory impairment in bvFTD (Glosser, Gallo, Clark, & Grossman, 2002). Our findings therefore build upon research which indicates that memory impairment in bvFTD may be driven by deficits in strategic organisational processes at the encoding level (Pasquier et al., 2001; Wicklund et al., 2006). Nonetheless, while value-directed selectivity appeared to be limited in bvFTD, future studies may benefit from additional indices of strategic

organisation during encoding. For example, analyses of serial order or item effects may provide further insights regarding recall performance during learning trials, and determine whether bvFTD patients show deficits in their capacity to recall high-value items first, to group together the four high-value items or to recall new words across trials.

Associations between value-directed selectivity and executive function

The second aim of this study was to examine the extent to which value-directed selectivity is associated with executive functions, including working memory, cognitive flexibility and verbal inhibition. The selectivity score was included as a measure of memory efficiency on the final learning trial, with higher scores indicating a bias towards recalling high-value words. Within bvFTD patients, lower selectivity on the final learning trial was strongly associated with poorer verbal inhibition. Inhibitory dysfunction is commonly reported in bvFTD (Bozeat, Gregory, Ralph, & Hodges, 2000; Hornberger, Piguet, Kipps, & Hodges, 2008; Krueger et al., 2009), and is associated with prefrontal cortex atrophy, particularly in the ventromedial regions (Hornberger, Geng, & Hodges, 2011; O'Callaghan et al., 2013). Atrophy in this region has also been associated with impaired episodic memory recall performance in bvFTD, though the mechanisms through which ventromedial prefrontal cortex functions impact on episodic memory remain to be established (Wong, Flanagan, Savage, Hodges, & Hornberger, 2014). Of relevance, studies of directed forgetting—where stimuli are presented with instructions to either 'remember' or 'forget'—also highlight the importance of prefrontally-mediated inhibitory functions for selective forgetting of 'to-be-forgotten' versus 'to-be-remembered' information (Anderson & Hanslmayr, 2014; Wylie, Foxe, & Taylor, 2008). In the same vein, the significant association between inhibitory function and value-directed selectivity in our study suggests that bvFTD patients may have difficulty selectively inhibiting the encoding of low-value words, in order to prioritize encoding of the high-value words.

In contrast, value-directed selectivity did not correlate with executive function in AD. While it is possible that selectivity is related to other executive functions that are not captured on our tests, previous reports indicate that this is not significantly associated with working memory capacity in AD (Castel et al., 2009). Nonetheless, the adaptations made to reduce task complexity in our study (e.g., repeated learning trials using the same stimuli) may have restricted the range of selectivity scores on Trial 3. Consistent with their improvements across learning trials in terms of preferential recall of high-value words, AD patients also

showed improvement in value-directed selectivity across the learning trials (see Appendix C). Related to this point, encoding selectivity in our control group also appeared to be unrelated to performance on executive measures, though this was likely due to ceiling effects. Finally, it is important to note that across all participant groups, encoding selectivity on the value-directed learning task was not associated with general episodic encoding capacity per se. Taken together, whereas our findings in bvFTD demonstrate a clear link between reduced value-directed selectivity and inhibitory dysfunction, similar associations were not evident in AD patients or controls, nor were there any associations between selectivity and encoding capacity.

Value-directed enhancement of episodic memory recall and recognition

The final aim of this study was to examine the impact of value-directed learning on measures of delayed recall, as well as recognition for the words and associated point values. Given the extremely low delayed recall performance in AD, it is difficult to draw conclusions regarding any differential effects of value-directed encoding on subsequent memory recall. While bvFTD patients recalled fewer overall words at on the delayed recall relative to learning trials, no clear effect of value was evident. Our results on the delayed free recall trial therefore indicate that value was not sufficient to reduce the significant episodic memory recall deficits in either AD or bvFTD. Conversely, control participants showed a clear value-directed enhancement effect on delayed free recall, such that they recalled more medium- and high-value words relative to low-value words. While previous studies have shown this effect on recognition memory (Castel et al., 2007), we demonstrate, for the first time, that this enhancement effect also benefits recall of higher value information following a short delay in healthy adults.

Our corrected word recognition results (i.e. hits – false alarms) showed a value-directed enhancement effect in AD patients. Overall, AD patients correctly recognised fewer words compared to controls, yet their word recognition performance was greater for high-value compared to low-value words. In contrast, although bvFTD patients also recognised fewer words relative to controls, this did not differ across conditions. Finally, although word recognition did not differ across conditions in controls, this appeared to be due to a ceiling effect. Taken together, our results suggest that value was not sufficient to enhance word

recognition accuracy in bvFTD patients or controls. Conversely, value-directed encoding enhanced word recognition performance in AD only.

On the other hand, both patient groups and controls showed value-directed enhancement of memory for the point values associated with each word. Our results in AD demonstrate, for the first time, that memory for episodic details may be supported by value-directed learning. This suggests that memory for highly valued information may persist despite the profound memory impairment in AD, in circumstances where sufficient cues are provided to support retrieval. Conversely, although bvFTD patients did not show preferential encoding of high-value words during the learning trials, a significant value-directed enhancement effect on points recognition accuracy was observed. Although this may initially seem counterintuitive given that value had no effect on learning performance, our results suggest that there may be a disconnection between the encoding and retention of high-value information and the ability to apply this information in order to maximise points during the immediate recall learning trials. While our correlational analyses indicated that reduced encoding selectivity was related to inhibitory dysfunction, an additional explanation may be that bvFTD patients were not sensitive to the motivational aspect of the reward values during the learning task. Indeed, reduced motivation is a diagnostic symptom of bvFTD (Rascovsky et al., 2011), and evidence indicates that these patients show altered sensitivity to primary and secondary rewards (Fletcher et al., 2015; Perry & Kramer, 2013; Perry, Sturm, Wood, Miller, & Kramer, 2015) and poor performance on value-based decision-making tasks (Kloeters et al., 2013; Strenziok et al., 2011). Conversely, symptoms of apathy are relatively less prevalent in AD compared to bvFTD (Chow et al., 2009), and these patient groups show divergent profiles of reward sensitivity (Perry et al., 2015). Nonetheless, as we did not include concurrent measures of reward sensitivity, whether motivation deficits differentially contribute to value-directed selective recall performance in bvFTD and AD requires confirmation in future studies.

Collectively, our results demonstrate that AD patients may have the capacity to learn and retain information that is associated with a high level of value or importance, providing there is adequate repetition when learning and support during retrieval. Importantly, this value-directed enhancement of learning and memory was observed despite the significant executive deficits present in this patient group. This has clinical implications for the implementation of memory retraining programs in AD, and highlights an important role for motivation in

memory. Unlike laboratory settings where degrees of importance are clearly assigned, however, in daily life one must initially determine the relative value of information encountered, before preferentially encoding highly valued information (Castel, McGillivray, & Friedman, 2012). As such, supporting the valuation process by emphasizing value or importance may benefit learning and memory for certain pieces of information in AD. Further investigations are required, however, to establish whether this value-directed enhancement effect persists over longer time delays.

In contrast, although bvFTD patients appear to learn and remember aspects of value-related information, they do not appear to apply this knowledge in a motivationally-salient context. As such, the provision of clear indicators of value or importance may not be sufficient to overcome the significant inhibitory deficits, which impact on preferential recall in these patients. Furthermore, encoding selectivity did not appear to be related to episodic memory encoding capacity in bvFTD. Additional research is needed in order to disentangle the contributions of altered reward sensitivity and inhibitory dysfunction on value-directed selectivity in bvFTD. One potential approach would be to contrast performance on a value-directed learning task against performance on a selective memory task without any value component, such as the item-method directed forgetting paradigm (Anderson & Hanslmayr, 2014). To circumvent the problem of impaired insight when eliciting self-reports of encoding strategy, future studies in bvFTD may also benefit from incorporating physiological measures of arousal, as evidence indicates that healthy adults show greater pupil dilation when studying words associated with higher point values (Ariel & Castel, 2013). From a broader clinical perspective, further characterisation of the impact of motivation on memory represents an important area of future inquiry, especially given the high prevalence of apathy in this patient group (Merrilees et al., 2013).

As discussed above, a potential limitation of our study design is that we did not include concurrent measures of sensitivity to value or motivation. Although earning points on the experimental task appeared to influence value-directed learning and memory in controls and AD patients, it is also possible that point values were insufficient to elicit similarly motivated responses in bvFTD. Future studies that incorporate more tangible rewards (e.g. money) may further elucidate the impact of different reward types on value-directed learning and memory in these patients. Furthermore, the inclusion of additional measures of executive function may help further elucidate relationships between value-directed selectivity and different

aspects of executive function. While neuroimaging analysis was beyond the scope of this study, future investigations would benefit from incorporating structural and functional imaging metrics to further elucidate the neurocognitive mechanisms underpinning value-directed learning and memory in these patient groups. A final issue to note is the relatively small sample size of our patient groups. Our findings should therefore be interpreted with this caveat in mind, and future examination of value-directed learning and memory in bvFTD and AD will be important for confirmation of these novel findings.

Conclusions

In summary, we have adapted a selective memory task to provide insights into value-directed learning and memory in bvFTD and AD patients. In doing so, we have revealed a relatively preserved capacity to preferentially learn and recognise high-value information in AD patients. While reduced value-directed selectivity was distinctly associated with inhibitory deficits in bvFTD, our findings also uncovered a mismatch between memory for rewarding information and the ability to apply this knowledge in order to maximise rewards. From a broader theoretical viewpoint, our findings provide important insights regarding value-directed memory processes, and highlight the importance of interactions between motivation and memory.

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Figure 1 (A) Example of words and associated points used in the VDM task. (B) Example of word presentation procedure during learning phase of the VDM task. (C) Example of word and points recognition questions in the test phase of the VDM task.

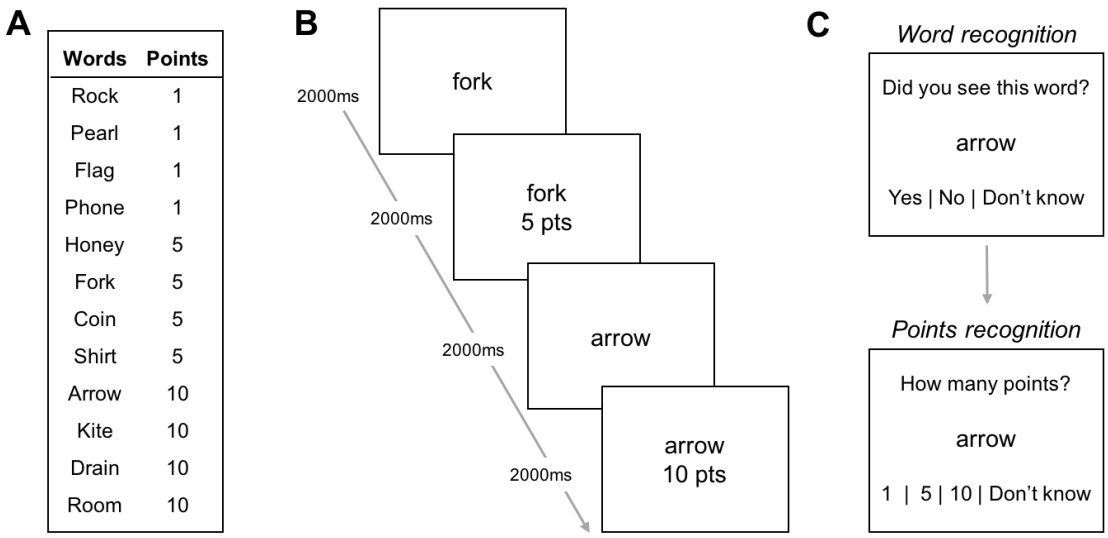

Figure 2 Number of low-, medium- and high-value words recalled across learning trials (A–C) and on the delayed recall trial (D) of the VDM task. Brackets indicate significant post hoc simple effects, *p< .05.

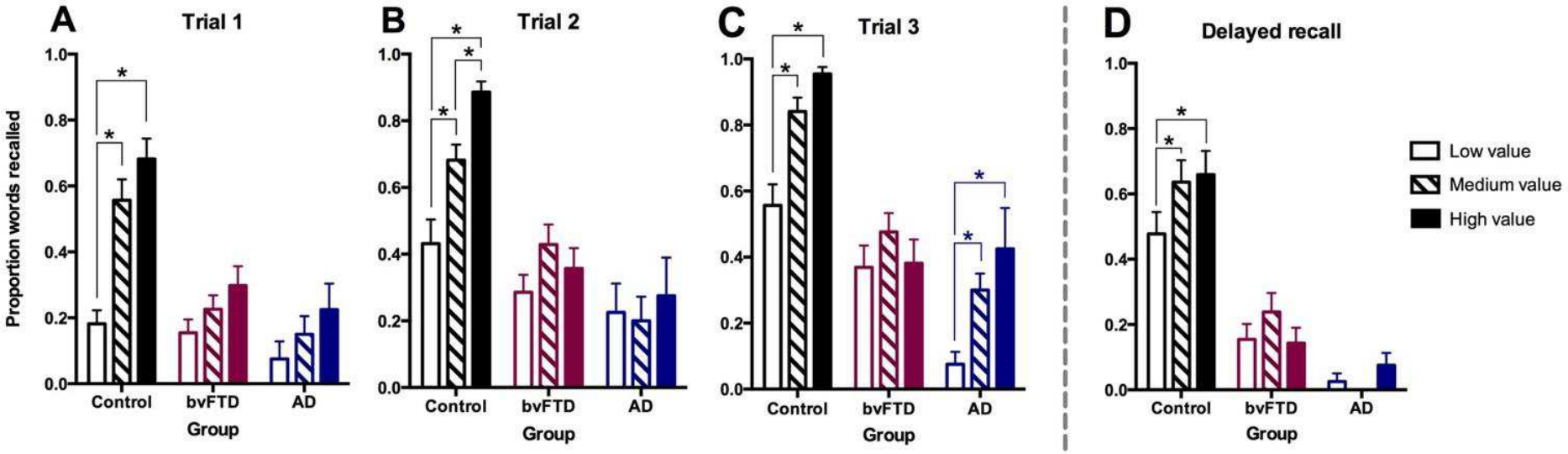

Figure 3 (A) Corrected word recognition (hits – false alarms) across conditions and groups on the word recognition test. (B) Points recognition accuracy for each condition across groups. Error bars represent standard error of the mean. Brackets indicate significant post hoc simple effects, *p< .05.

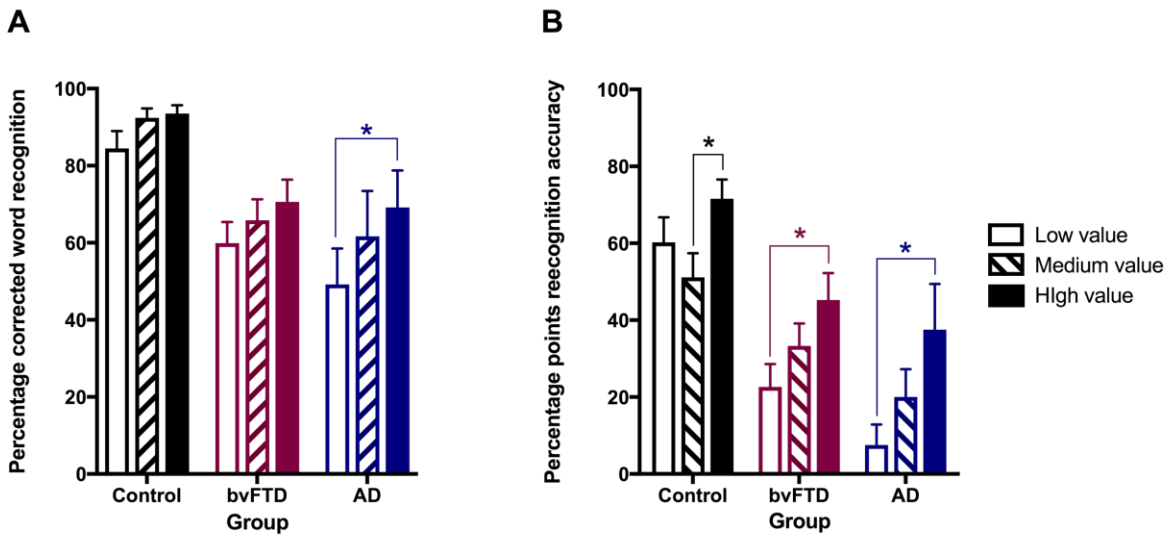

Table 1. Demographic and clinical characteristics and performance on neuropsychological measures of executive function and episodic memory[a]

	Control	AD	bvFTD	Group effect	Control vs. bvFTD	Control vs. AD	bvFTD vs. AD
Sex (M:F)	10:12	6:4	14:7	n.s.			
Age (years)	64.12 (6.82)	67.84 (9.12)	61.50 (7.13)	n.s.			
Education (years)	13.81 (2.43)	12.33 (2.86)	11.35 (2.29)	**	**	n.s.	n.s.
Disease duration (years)		6.48 (4.99)	5.58 (3.22)	n.s.			
CDR SoB [18]		5.28 (1.39)	5.26 (3.22)	n.s.			
FRS Rasch score		0.27 (1.14)	−0.69 (1.31)	#			
ACE-III [100]	96.23 (3.58)	60.80 (12.14)	74.00 (13.05)	***	***	***	n.s.
DSB [15]	8.68 (1.99)	4.5 (2.07)	4.52 (1.47)	***	***	***	n.s.
TMT B − A time (seconds)	39.05 (16.66)	240.42 (149.04)	121.71 (103.78)	***	***	***	n.s.
Hayling AB error score [128]	2.77 (4.92)	12.43 (6.80)	23.06 (18.66)	***	***	**	n.s.
RAVLT learning trials							
Trial 1 [15]	6.73 (2.05)	2.78 (1.56)	4.25 (1.61)	***	**	***	n.s.
Trial 2 [15]	9.91 (2.65)	3.89 (0.93)	5.75 (2.32)	***	***	***	n.s.
Trial 3 [15]	11.68 (2.40)	5.33 (2.12)	7.44 (2.68)	***	***	***	n.s.
Trial 4 [15]	12.73 (1.70)	4.89 (2.42)	7.69 (2.60)	***	***	***	n.s.
Trial 5 [15]	13.14 (1.75)	4.44 (2.19)	8.31 (3.59)	***	**	***	n.s.
RAVLT 30-minute recall [15]	10.32 (2.99)	1.56 (1.67)	4.94 (3.04)	***	**	***	n.s.
RAVLT corrected recognition [15]	12.09 (2.81)	− 2.44 (7.25)	2.56 (5.75)	***	***	***	n.s.

[a] Standard deviations in parentheses, maximum score for tests shown in brackets.

Clinical Dementia Rating Scale (CDR); Frontotemporal Dementia Rating Scale (FRS); Addenbrooke's Cognitive Examination (ACE-III); Digit Span Backwards (DSB); Trail Making Test (TMT); Rey Auditory Verbal Learning Test (RAVLT).

*p<.05; **p<.01 ; ***p<.001 ; n.s. = non-significant; #=trend, p=.066

Table 2. Spearman rank correlation coefficients from analyses exploring associations between selectivity index scores on Trial 3 of the VDM task and performance on neuropsychological measures of executive function and verbal episodic memory encoding.

	Executive function			Verbal episodic memory encoding
	DSB total	**TMT B-A time[a]**	**Hayling AB error score[a]**	**RAVLT Trial 5 total**
Controls	–0.140	–0.093	0.047	0.045
AD	0.387	–0.357	–0.019	0.355
bvFTD	0.382	–0.416	**–0.560***	0.334

[a]Higher scores denote greater impairment.

Values are Spearman correlation one-tailed t tests. *p=0.01.