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Executive functioning in Alzheimer's disease and vascular dementia†

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†This is an original work which has not been published elsewhere or submitted for publication elsewhere. A paper on attention deficits in the same cohort of patients has been accepted to JNNP and is currently in print (McGuinness *et al*.). There is however no overlap between the neuropsychological tests used and it has been referenced in the discussion.

Objective: To compare performance of patients with mild-moderate Alzheimer's disease (AD) and vascular dementia (VaD) on tests of executive functioning and working memory.

Methods: Patients with AD ($n = 76$) and VaD ($n = 46$) were recruited from a memory clinic along with dementia free participants ($n = 28$). They underwent specific tests of working memory from the Cognitive Drug Research (CDR) battery and pen and paper tests of executive function including CLOX 1 & 2, EXIT25 and a test of verbal fluency (COWAT). All patients had a CT brain scan which was independently scored for white matter change/ischaemia.

Results: The AD and VaD groups were significantly impaired on all measures of working memory and executive functioning compared to the disease free group. There were no significant differences between the AD and VaD groups on any measure. *Z*-scores confirmed the pattern of impairment in executive functioning and working memory was largely equivalent in both patient groups. Small to moderate correlations were seen between the MMSE and the neurocognitive scores in both patient groups and the pattern of correlations was also very similar in both patient groups.

Conclusions: This study demonstrates sizeable executive functioning and working memory impairments in patients with mild-moderate AD and VaD but no significant differences between the disease groups.

Key words: executive function; Alzheimer's disease; vascular dementia; working memory
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Introduction

Accurate diagnosis of Alzheimer's disease (AD) and vascular dementia (VaD) can be a difficult clinical challenge. Explicit memory deficits are core to the diagnosis of AD due to early pathology in medial temporal-limbic systems. However, increasingly it has been recognized that problems with executive functioning, including working memory, occur early in the disease process as pathology spreads to the neocortical association areas involving the temporoparietal and prefrontal cortices (Tomlinson *et al.*, 1970; Braak and Braak, 1991). In VaD, pathology can be patchy but frequently involves the frontal subcortical circuit including the dorsolateral prefrontal neuronal circuit that mediates executive functioning and working memory (Cummings *et al*., 1987).

Executive function refers to those higher cognitive activities by which performance is optimized in situations requiring the simultaneous operation of several cognitive processes (Baddeley, 1992). Executive functions control the planning, sequencing and execution of complex goal-directed activities such as cooking, dressing, shopping and housework (Lezak,

1983). These are highly dependent on the short-term working memory system which allows information to be held and manipulated in mind during effortful tasks including learning, reasoning and comprehending (Baddeley and Hitch, 1974). A central executive is seen as coordinating the operation of two subsidiary slave systems, the phonological loop which deals with speech based information, and the sketchpad which handles visuo-spatial information. A defective executive such as this occurs with executive control function deficits will lead to difficulty coordinating the simultaneous operation of these two systems.

A recent review from the Committee on Research of the American Neuropsychiatric Association reported it is likely that measures of executive functioning such as the Executive Interview [EXIT25] (Royall *et al*., 1992) and the face/hand test are relatively strong correlates of functional capacities, particularly medical and financial decision making (Royall *et al*., 2007) and hence, impairments in this neurocognitive domain are likely to impact an individual's ability to live independently. This then leads to increased rates of institutionalization and health care costs. A strong relationship has been demonstrated between functional impairment and health care costs in patients with dementia (Hill *et al*., 2006).

The literature regarding impairments of executive function in AD and VaD has been inconsistent. Initially, neuropsychological studies pointed towards patients with VaD performing better on memory tests and worse on tests of executive function compared to patients with AD (Mendez and Ashla-Mendez, 1991; Villardita, 1993). A meta-analysis showed that patients with VaD had greater impairment in frontal executive functioning compared to AD patients but it was accepted that the studies included may have had difficulties with uncertainty in diagnostic criteria for VaD, possible inclusion bias and possible overlap of AD and VaD among other methodological shortcomings (Looi and Sachdev, 1999). A more recent sizeable study (AD group $n = 307$; VaD group $n = 168$) showed that executive deficits were prevalent in both disease processes and a call was made to reconsider deficits of executive function as a core feature of dementia (Voss and Bullock, 2004). A further study in patients with mild AD found executive impairments were common but there was considerable heterogeneity among AD patients in the pattern of executive dysfunction (Stokholm *et al*., 2006).

As an added complication, it has been suggested that AD and VaD are on a continuum, with many patients having elements of both, and emphasis has now switched to identifying commonalties in these diseases' cognitive profiles. In the following study, we aimed to examine the profile of executive functioning in patients with mild-moderate AD and VaD to determine whether executive impairments are present at an early stage in both disorders.

Methods

The Research Ethics Committee of the Queen's University Belfast approved this study (Application Number 249/03). Written informed consent was obtained from all participants and assent from carers was obtained if necessary. The 150 participants in the study (VaD = 46, AD = 76) were recruited from the memory clinic at the Belfast City Hospital. Disease-free participants (DF, $n = 28$) were also recruited from the memory clinic to provide normative data: they presented as referrals or spouses of patients. DF participants had no evidence of depression or cognitive impairment on detailed questioning or on neuropsychological testing.

Patients were assessed using a structured interview, physical examination, routine biochemical screening and CT scan of brain. A detailed corroborative history was taken from the carer (usually a family member). A diagnosis of probable AD or probable VaD was made using the NINCDS-ADRDA (McKhann *et al*., 1984) and NINDS AIREN (Roman *et al*., 1993) criteria, respectively. Only patients with MMSE ≥ 12 were included as we were primarily interested in executive function deficits in patients with mild-moderate disease. Patients with findings suggestive of mixed dementia, Lewy body dementia and/or an additional standardized diagnosis of depression were excluded from the study. No patients were being treated with cholinesterase inhibitors at the time of testing. Two rating scales were used to quantify the site and severity of white matter changes and cerebrovascular disease on images available for AD and VaD patients: White Matter Scale (WMS, van Swieten *et al*., 1990) and an adapted Image Criteria Score (aICS, Pullicino *et al*., 1996). These scores were calculated by a single experienced radiologist blinded to the clinical diagnosis of the patient.

Neuropsychological evaluation

Premorbid IQ was estimated using the National Adult Reading Test (NART, Nelson and O'Connell, 1978).

Working memory was assessed using tests from the CDR battery (www.cognitivedrugresearch.co.uk): a

numeric working memory (NWM) task assessed the articulatory loop sub-system of working memory and a spatial working memory (SWM) task assessed the visuo-spatial sub-loop of working memory (Baddeley and Hitch, 1974). Mean speed on the SWM and NWM tasks along with a sensitivity index, were recorded. The sensitivity index was calculated from the formulae derived by Frey and Colliver (1973): it combines accuracy scores from familiar as well as novel (distractor) information contained within the tasks. By combining the ability to identify previously presented items and to correctly reject items that were not previously presented, it represents the ability of the participant to discriminate (or be sensitive to) the task information. The scores ranged from 0–1, and a score of 1 represented perfect discrimination.

Pen and paper tests were also used to assess executive function. These were: the Executive Interview [EXIT25] (Royall *et al*., 1992), Clock Drawing [CLOX 1 and 2] (Royall *et al*., 1998) and the Controlled Oral Word Association Test [COWAT] of verbal fluency (Benton *et al*., 1983).

EXIT 25: This is a general interview containing 25 items and is a clinically based bedside screen for executive functioning impairments. It was specifically designed to predict impairments in self-care and functional status (Royall *et al*., 1992). Each item is scored from 0 (intact) to 2 (specific incorrect response or failure to perform a task). A score >15 indicates executive impairment.

The CLOX is divided into two parts. CLOX 1 specifically assesses executive control; the participant was instructed to 'draw me a clock that says 1.45, set the hands and numbers on the face so a child could read them'. CLOX 2 is a simple copying task that generally identifies posterior cortical deficits. Lower scores on the CLOX reflect greater impairment.

COWAT: Participants generated words beginning with each of the letters F, A and S, and were allowed 1 min per letter. They then listed as many items belonging to a given semantic category as possible (animals) in 1 min to test semantic fluency. This allowed for average phonological, or letter, fluency performance to be contrasted with semantic fluency performance. The former is highly dependent on executive functioning systems while the latter is more dependent on semantic memory systems (Benton *et al*., 1983).

Statistical analysis

Study data were analysed using SPSS Version 15 (Chicago, IL, 2008). The groups' demographic data were compared using one-way analysis of variance [ANOVA]. Missing neurocognitive data ($<5\%$) were imputed using the expectation-maximization method. The performance of the DF, AD and VaD groups on tests of executive functioning was then compared using analysis of covariance [ANCOVA], with Bonferroni corrected *post hoc* multiple comparisons used to detail group differences. Covariates considered in these models were age and years of education because patient groups significantly differed from DF participants on these variables. Potential gender differences between groups were also considered but this factor had no significant main effect nor did it interact with the groups and hence, was not retained in the ANCOVA models. *Z*-scores adjusted for age and education were also calculated for each of the measures relative to the DF groups' performance. Pearson's correlations were also carried out to examine the relationship between measures of executive function and the MMSE.

Results

Demographics for the groups are shown in Table 1. AD and VaD groups did not significantly differ in terms of age, sex, education, NART or MMSE.

Table 1 Characteristics of patients and disease-free participants

	Disease-free	AD	VaD	ANOVA			Multiple comparisons
	$n=28$	$n=76$	$n=46$	F	df	p	
Age (years; mean (SD))	70.2 (7.9)	77.7 (6.8)	75.9 (7.3)	0.52	2,147	0.60	DF < AD**; DF < VaD**
MMSE (mean (SD))	29.4 (0.8)	22.5 (3.3)	22.2 (3.8)	13.53	2,147	< 0.01	DF > AD**; DF > VaD**
Education (years; mean (SD))	13.6 (3.4)	11.3 (1.9)	15.2 (2.2)	9.74	2,147	< 0.01	DF > AD**; DF > VaD**
NART IQ (mean (SD))	119.6 (6.8)	109.4(8.6)	109.6 (7.5)	1.41	2,144	0.25	DF > AD*; DF > VaD*
Gender F:M	15:13	52:24	24:22	$\chi^2=3.9$	2	0.14	

*Significant $p<0.05$; **Significant $p<0.01$.

Table 2 Radiological measures in patients and disease-free participants

		Disease free	AD	VaD	Mann–Whitney U^a	
		$n = 28$	$n = 76$	$n = 46$	U	p
WMS	n (0–2:3–4)	18:0	60:8	17:24		
	% (0–2:3–4)	100:0	88.2:11.8	41.4:58.6		
	Median (IQR)	0 (0–2)	1 (0–2)	3 (1.25–4)	350	< 0.01
aICS	n (0–1:2–3)	18:0	65:3	16:25		
	% (0–1:2–3)	100:0	95.5:4.5	39:61		
	Median (IQR)	0 (0)	0 (0)	2 (1–2)	585	< 0.01

WMS: White Matter Scale.
aICS: Adapted Image Criteria Score.
[a]Comparisons between patient groups only.

Despite best efforts to match cases and DF participants, there was a significant difference between the disease groups (AD and VaD) and the DF group in terms of age, years of education and NART IQ. This was controlled for in further analyses. Comparisons between radiological scores revealed significantly more cerebrovascular disease in the VaD group relative to the AD group ($p < 0.01$) confirming the clinical diagnoses (Table 2).

Table 3 shows results from the neurocognitive tests. The AD and VaD groups were significantly impaired on all measures of working memory and executive functioning relative to the DF group. However, there were no significant differences between the AD and VaD groups on any measure. CLOX 2 was controlled for when analysing CLOX 1, there remained a significant difference between the DF group and the disease groups ($p < 0.01$) but no significant difference was seen between the AD and VaD groups ($p = 1.0$).

Z-scores confirmed that the pattern of impairment was largely equivalent in both patient groups. The greatest impairment was seen on the general interview EXIT25 (*Z*-score 3.29 and 3.90 in the AD and VaD groups, respectively) notwithstanding greater variability in performance in the patient groups. NWM reaction time was considerably more impaired in both AD and VaD (*Z*-scores 2.74 and 3.40, respectively) compared to SWM reaction time (*Z*-scores 1.34 and 1.14, respectively). With respect to the sensitivity indices however, the opposite was seen with greater impairment in the SWM sensitivity index (*Z*-scores 2.76 and 3.40 in AD and VaD groups, respectively) compared to the NWM sensitivity index (*Z*-scores 1.29 and 1.44 in the AD and VaD groups, respectively). Greater impairment in visuospatial executive functioning was also observed on other tests: verbal fluency was relatively less impaired compared to CLOX performance.

With the exception of the COWAT, the patient groups showed greater variability in their performance of the neurocognitive tests compared to DF participants. An examination of correlations (Table 4) between the MMSE and neurocognitive scores showed that they were small to moderate in size. Notably, the pattern of correlations was also very similar in both dementia groups.

Post hoc analyses of patients with (i) MMSE > 20 and (ii) MMSE > 24 were then conducted to confirm that patients with moderate dementia were not overly influencing primary findings. Patient groups did not significantly differ on any measure in these analyses. In patients with an MMSE > 20, there were significant differences between the DF and dementia groups across all tests of executive functioning and working memory. However, there was no longer a significant difference between the DF and AD or VaD groups on NWM reaction time ($p = 0.09$, $p = 0.07$), respectively or between the DF and VaD group on SWM reaction time ($p = 0.15$).

When patients with mild dementia (MMSE > 24) were analysed alone, numbers were small (AD $n = 22$, VaD $n = 13$). Again there was a significant difference between the DF and AD and VaD groups on performance on the majority of neurocognitive indices apart from SWM reaction time in the AD ($p = 0.06$) and VaD ($p = 0.08$) groups and the DF and VaD group on CLOX 1 and 2 ($p = 0.32$, $p = 0.24$, respectively).

Discussion

In this study, we found sizeable executive functioning and working memory impairments in patients with mild–moderate AD and VaD. We did not demonstrate any differences between the disease groups. This is in keeping with a previous study in which executive

Table 3 Executive functioning in patients and disease-free participants

Measure	Disease free $n = 28$	AD $n = 76$		VaD $n = 46$		ANCOVA			Multiple comparisons
	Mean (SD)	Mean (SD)	Z (SE)[a]	Mean (SD)	Z (SE)[a]	F	df	p	
SWM reaction time (ms)	1482.4 (1013)	2874.5 (1898)	1.34 (0.19)	2635.2 (1461)	1.14 (0.24)	4.76	2,145	0.01	AD > DF**; VaD > DF*
SWM sensitivity index	0.87 (0.18)	0.36 (0.35)	2.76 (0.21)	0.40 (0.35)	2.59 (0.27)	16.6	2,145	< 0.01	AD < DF**; VaD < DF**
NWM reaction time (ms)	1018.9 (217)	1626.9 (878)	2.74 (0.50)	1774.2 (1166)	3.40 (0.62)	4.18	2,145	0.02	AD > DF*; VaD > DF**
NWM sensitivity index	0.97 (0.1)	0.84 (0.2)	1.29 (0.25)	0.82 (0.2)	1.44 (0.31)	3.7	2,145	0.03	AD < DF*; VaD < DF*
Letter fluency	14.4 (5.0)	9.3 (3.9)	0.95 (0.09)	7.8 (3.2)	1.26 (0.11)	13.1	2,145	< 0.01	AD < DF**; VaD < DF**
Semantic fluency	15.8 (4.6)	9.5 (3.8)	1.29 (0.10)	9.2 (3.5)	1.39 (0.12)	15.2	2,145	< 0.01	AD < DF**; VaD < DF**
EXIT 25	7.8 (2.6)	16.8 (5.6)	3.29 (0.22)	18.2 (5.4)	3.90 (0.28)	23.4	2,145	< 0.01	AD > DF**; VaD > DF**
CLOX1 (executive)	12.6 (1.7)	8.8 (2.5)	2.17 (0.18)	9.0 (3.1)	2.10 (0.22)	14.1	2,144	< 0.01	AD < DF**; VaD < DF**
CLOX2 (visuospatial)	14.1 (1.2)	10.9 (2.6)	2.51 (0.24)	11.0 (3.0)	2.54 (0.31)	8.7	2,144	< 0.01	AD < DF**; VaD < DF**

[a]Adjusted for age and education.
*$p < 0.05$; **$p < 0.01$.

functioning impairments were similar in AD and VaD patients (Voss and Bullock, 2004) adding further doubt to the assertion that VaD is associated with greater executive functioning impairment compared to AD. Strengths of the study include good sample size, clinical diagnosis confirmed by independently rated formal criteria based on both clinical and neuroradiological information and group matching by dementia severity (MMSE) and mood (depressed cases excluded). The major limitation was the difference in age and education between the disease group and the DF group; these were controlled for, however, in all analyses.

We assessed both verbal and visuospatial working memory in these patients and noted an interesting dissociation. Verbal performance was less impaired than visuospatial functioning, but possibly at the expense of the speed at which verbal information was processed. However, the relative simplicity of the NWM task may account for this finding: scores on this task may have been subject to a ceiling effect. The sensitivity index in the DF group was close to 1.0 (0.97) reflecting almost perfect discrimination between the original and the novel (distractor) information. In the AD and VaD groups the sensitivity indices were also high (0.84 and 0.82, respectively) compared to values for both in the SWM task (0.36 and 0.40, respectively). However, patients were also relatively less impaired on the speeded verbal fluency task compared to the non-speeded visuospatial CLOX task. This would collectively suggest that working memory and executive functions that are more reliant on visuospatial skills are more susceptible to disruption in the early stages of both AD and VaD. Regarding verbal fluency, it is generally expected that semantic fluency scores will exceed letter fluency scores in healthy volunteers, but this pattern is disrupted in AD due to memory impairments resulting in poorer semantic fluency (Graham *et al*., 2004; Lezak *et al*., 2004). The evidence to support this assertion in this study was relatively weak. When patients with moderate dementia were excluded from the analysis working memory processing speed differences between the DF and dementia groups were less significant especially in the VaD group but other impairments remained. When only those with mild dementia were analysed there remained sizeable differences between the DF and dementia groups. The lack of significance between the DF and VaD group on CLOX 1 and 2 may have been predicted by the moderate correlation with MMSE.

Working memory and executive control function are inter-related and we have demonstrated impairments in both AD and VaD. Deficits in executive function increase the likelihood of impairments on a

Table 4 Correlations with MMSE

	SWM reaction time	SWM sensitivity index	NWM reaction time	NWM sensitivity index	Letter fluency	Semantic fluency	EXIT 25	CLOX1	CLOX2
AD	−0.15	0.32**	−0.24*	0.33**	0.32**	0.42**	−0.58**	0.48**	0.55**
VaD	−0.12	0.41**	−0.39**	0.35*	0.33*	0.42**	−0.64**	0.45**	0.59**

*$p < 0.05$; **$p < 0.01$.

wide range of activities such as driving, cooking and handling finances. Authors have speculated that executive functioning impairment is distinct from memory impairment and may independently contribute to both the rate of decline and the functional impact of the dementia (Thompson *et al*., 2005). Within executive function, sequencing and planning appear to be more predictive of functional loss than cognitive speed (Srikanth *et al*., 2005): hence, tests such as EXIT25 and CLOX may be more informative in terms of functional loss. Mean scores from the EXIT25 interview in particular indicated that executive impairments were clinically significant in these patient groups, suggesting that patients' capacity for self-care should be of genuine concern, even in the early stages of these disease processes. However, the sizeable correlations between the EXIT25 and MMSE in particular would indicate that executive impairment is also highly related to the severity of patients' dementia.

In conclusion, we have previously demonstrated deficits in attention in this cohort of patients (McGuinness *et al*., in print) and now find deficits in executive function and working memory in patients with mild-moderate AD and VaD that are similar in magnitude in both groups. This lends weight to the proposal that AD and VaD are on a continuum and emphasises commonalities in their cognitive profiles. To further this research we propose that functional abilities (both basic and instrumental activities of daily living (ADLs)) are routinely measured along with executive function and working memory in a memory clinic setting. These are likely to contribute to estimation of decline in patients with mild to moderate AD and VaD. Furthermore, we propose to identify explanatory factors that contribute to the heterogeneity in patients' performance of executive tasks. It would also be of interest to examine the executive/memory ratio in patients with AD and VaD as it may be this ratio rather than the size of executive functioning deficits *per se* that differentiates patients with AD from patients with VaD.

Key points

- Deficits demonstrated in executive functioning and working memory in patients with mild to moderate AD and VaD.
- No difference in deficits in executive functioning or working memory between AD or VaD patients.

Conflict of interest

None.

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