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Working memory in Alzheimer's disease and frontotemporal dementia

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1. Background

Working memory deficits are a recognised feature of Alzheimer's disease (AD) and can be dissociated from episodic memory impairment, with distinct patterns of breakdown in individuals [1]. Distinctions in clinical profile may have neurobiological relevance. We have previously shown [2] that patients presenting with a dense yet relatively circumscribed classical amnesia ("amnestic-AD", accounting for 10% in a series of 523 patients) were older and more likely to carry apolipoprotein $\varepsilon 4$ alleles than those presenting with a constellation of working memory, language and perceptuospatial deficits (labelled "typical- AD" on the basis that they accounted for 61% of cases). Such findings highlight the importance of careful characterisation of individual patients in experimental research. A goal of the present study was to understand the working memory deficit in AD whilst recognising these important distinctions. Existing research focuses on difficulties on dual-task paradigms, encouraging the notion of central executive dysfunction, and promoting a relationship between working memory deficits and frontal lobe pathology in AD [3]. Failures on standard tests of attention and executive function reinforce this interpretation. However, characteristic neuroimaging changes in early onset AD are in posterior hemispheres rather than frontal lobes. Moreover, 'frontal' behavioural characteristics are absent. Characteristic qualities of persistence, motivation, and concern for accuracy contrast markedly with the economy of effort and lack of engagement demonstrated by patients with frontotemporal dementia (FTD), the prototypical neurodegenerative disease of the frontal lobes. The presence of qualitative differences in cognitive profile [4] suggests that there are distinct contributions to performance failure. We took the novel approach of exploring the frontal dysexecutive contribution to working memory by comparing test performance in patients with AD and FTD. If the basis of the impairment is primarily 'frontal dysexecutive', then one would expect similar profiles in the two groups. However given the 'posterior' abnormalities shown on AD patients' imaging and absence of 'frontal' behavioural signs, we predicted that there ought to be qualitative differences on tests of working memory, attention, and executive function.

2. Participants

In line with our earlier work [2], the main focus were "typical" patients ($n = 20$; age 52–68) presenting with a constellation of cortical symptoms. Those with a circumscribed "amnesic" presentation ($n = 18$; age 59–83) were included as a reference group. AD patients were classified based on clinical history of symptoms obtained at initial diagnostic assessment and performance on a locally developed neuropsychological screening assessment. There were no significant differences between the AD and FTD patients ($n = 26$; age 52–76) with regard to illness duration (4–6 years) or Clinical Dementia Rating scale score (CDR 1: mild). Clinical neuroimaging showed characteristic temporoparietal change in typical-AD, medial temporal changes in amnesic-AD, and frontal lobe abnormalities in FTD.

3. Methods

Tasks were administered to examine working memory (a modified Brown-Peterson test involving memory for three words with and without delay/distraction;

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Table 1

Task	Measure	Result	Comment
Working memory			
Modified working memory test	Overall accuracy	Typ-AD < FTD < Amn-AD = control	Poorer performance in Typ-AD than other groups
	No distraction, no delay	Typ-AD < FTD = Amn-AD = control	Typ-AD impaired even without distraction or delay
	With delay	Typ-AD < FTD = Amn-AD = control	FTD impaired only when distraction present
	With distraction	Typ-AD < FTD < Amn-AD = control	Amn-AD performance normal
Digit span	Forward and reverse	Typ-AD = FTD < Amn-AD = control	Span impaired in Typ-AD and FTD but not Amn-AD
	Sequencing Errors	FTD > Typ-AD	More sequencing errors in FTD
Body part pointing	Accuracy: 4 body parts	Typ-AD < FTD < Amn-AD = control	Poorer performance in Typ-AD than other groups
	Omission errors	Typ-AD > FTD	Typ-AD more prone to omission error (“forgetting” items),
	Sequencing errors	FTD > Typ-AD (trend)	FTD show tendency to misorder items
Phonological similarity task	Overall letter span	Typ-AD = FTD < Amn-AD = control	Reduced letter span in both Typ-AD and FTD
	Phonological Similarity effect	Absent in Typ-AD; Present in others	Normal phonological similarity effect in FTD but not Typ-AD.
Word length	Overall word span	Typ-AD < FTD = Amn-AD = control	Reduced word span in Typ-AD only
	Word length effect	Present in all groups	Span affected by word length in all groups
Visual patterns	Visual span	Typ-AD = FTD < Amn-AD = control	Reduced visual span in both Typ-AD and FTD
Attention			
Vigilance A: sustained attention	Detection accuracy	FTD < Typ-AD = Amn-AD = control	FTD impaired accuracy, Typ-AD perform normally
	Presentation speed effect	More errors with faster presentation speed in patient groups, not controls	Accuracy in all patient groups affected by presentation speed
	Reaction time	Typ-AD = FTD = Amn-AD = control	Speed of response normal in all groups
Vigilance B: continuous performance	Overall accuracy	Typ-AD = FTD < Amn-AD = control	Typ-AD and FTD both show impaired accuracy
	Reaction time	Typ-AD = FTD = Amn-AD = control	Response times normal in all groups
	Loss of track of task	Typ-AD present; FTD absent	Behavioural observations show loss of track in Typ-AD and distractibility in FTD
	Distractible behaviour	FTD present; Typ-AD absent	
Executive Function			
Go-No-Go	Inhibition (no-go) errors	FTD > other groups	FTD make most ‘no-go’ responses and show marked effect of ‘Go’ to ‘No-go’ ratio
	Effect of Go:No-go ratio	FTD > other groups	Both Typ-AD and FTD omit targets
	Omission (go) errors	Typ-AD = FTD < Amn-AD = control	Amn-AD perform normally
Set switching	Accuracy	FTD < Typ-AD < Amn-AD < control	Impaired set switching in all patient groups, worst in FTD
	Response time	Typ-AD < Amn-AD < FTD = control	Response times slowed in Typ-AD and Amn-AD, not FTD
	Loss of track	Typ-AD present; FTD absent	Typ-AD lose track, request repetition of instructions
	Erratic, impulsive responses	FTD present; Typ-AD absent	FTD show erratic responding with poor use of feedback

verbal digit, letter and word span tasks with phonological similarity and word length comparisons; pointing to body parts in order; visual pattern span test requiring memory of filled and unfilled squares on a grid); attention (sustained response to serial presentation of a single stimuli and a continuous performance task involving response to a designated stimuli among serially presented items); and executive function (a go:no-go inhibition task and a two-rule set-shifting task).

4. Results

Both typical-AD and FTD groups were impaired across tasks. Amnesic-AD patients performed well. Despite some similarities in overall score, typical-AD and FTD patients showed distinct performance profiles (Table 1). AD patients showed a profound deficit in repetition span, even on tasks without a dual-task component. They made omission errors and showed abnormal phonological similarity effects. FTD patients had difficulty on distraction tasks and made sequencing errors. Whereas FTD patients performed poorly on both sustained and continuous performance attentional tasks, AD patients were only impaired on the latter, the principal methodological difference being the amount of sequential information to be processed. On the go:no-go task typical-AD patients omitted both 'go' and 'no-go' targets, and asked for repetition of task instructions. The FTD group both omitted 'go' targets and made inhibition errors. On the set-shifting task both groups were impaired but typical-AD patients completed the task slowly and carefully. FTD patients responded quickly, and did not utilise feedback.

5. Discussion

Although both typical-AD and FTD groups were impaired across tasks, differences in profile suggest contrasting underlying deficits. 'Dysexecutive' features displayed in FTD (e.g. impaired inhibition, failure to use feedback, striking inattention) were absent in the AD group, who showed profound problems in working memory span and were consistently compromised when load was increased. These differences would be consistent with the notion that there are alternative, non-frontal contributions to the working memory problems in AD.

Verbal span deficits suggest a phonological contribution. Phonological impairments are reported by some authors (e.g. [5]), but there is a propensity to attribute such profiles to greater disease severity [6]. We would argue against this interpretation. Patients with severe span deficits are typically younger and demonstrate a distinct pattern of cortical symptoms. Illness duration and CDR scores were similar among all patient groups. We therefore propose that working memory problems are part of the posterior cortical symptomatology typical of youthful presentations of AD.

The typical-AD group also showed reduced visual span, suggesting that deficits cannot be entirely phonologically based. Span tasks were carried out in isolation, so deficits cannot be attributed to dual task impairment, as argued for other cohorts (e.g. [3,7]). Our data therefore suggest specific impairments in phonological and visuospatial short-term capacity and processing, rather than the central executive component of working memory. Notably, the deficit bears resemblance to that of 'short-term memory' patients (e.g. [8]), who, like this AD cohort, have lesions in temporoparietal cortex. Accumulating neuroimaging evidence further suggests a role for the posterior cortices in binding, retrieval, manipulation, and storage (e.g. [9]). The present study thus highlights the multiple contributions that may be involved in working memory deficits in AD, both pointing to a need for caution in the 'dysexecutive' interpretation of test failures and highlighting the potential role of the posterior hemispheres. They underline also the phenotypic variation within AD.

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