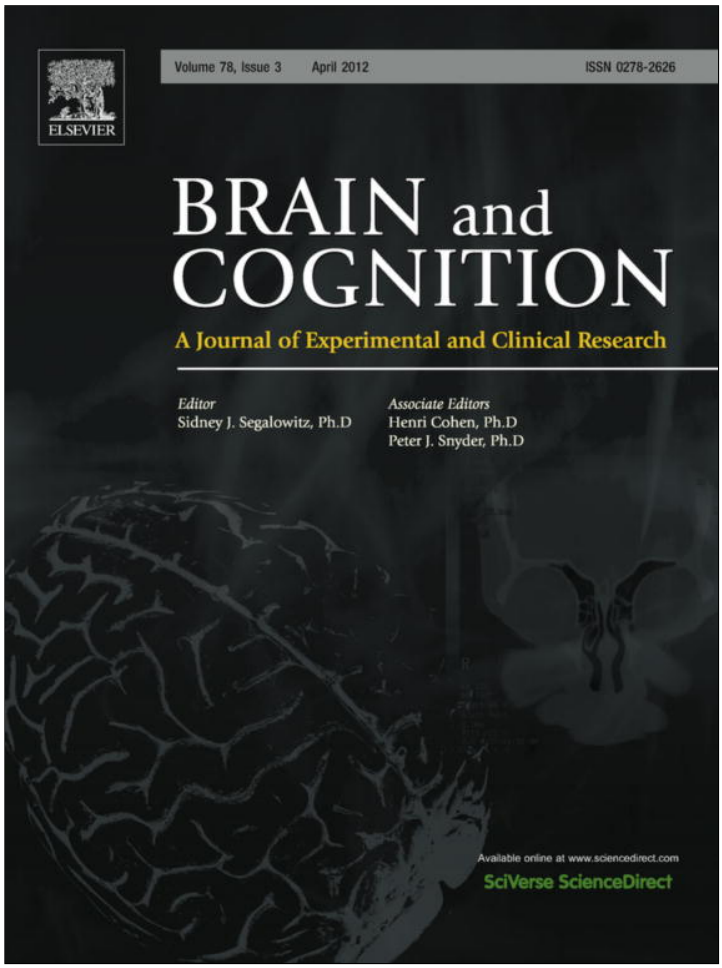

Brain and Cognition 78 (2012) 189–199

Contents lists available at SciVerse ScienceDirect

Brain and Cognition

journal homepage: www.elsevier.com/locate/b&c

Insights into spared memory capacity in amnestic MCI and Alzheimer's Disease via minimal interference

Michaela Dewar [a,*], Martina Pesallaccia [b], Nelson Cowan [c], Leandro Provinciali [b], Sergio Della Sala [a]

[a] Human Cognitive Neuroscience and Centre for Cognitive Ageing and Cognitive Epidemiology, Psychology, University of Edinburgh, Edinburgh, UK
[b] Department of Neuroscience, Polytechnic University of Marche Medical School, Ancona, Italy
[c] Department of Psychological Sciences, University of Missouri, -Columbia, USA

ARTICLE INFO

Article history:
Accepted 6 December 2011
Available online 17 January 2012

Keywords:
Amnestic Mild Cognitive Impairment (aMCI)
Alzheimer's Disease (AD)
Long Term Memory (LTM)
Consolidation
Memory interference
Spared memory capacity

ABSTRACT

Impairment on standard tests of delayed recall is often already maximal in the aMCI stage of Alzheimer's Disease. Neuropathological work shows that the neural substrates of memory function continue to deteriorate throughout the progression of the disease, hinting that further changes in memory performance could be tracked by a more sensitive test of delayed recall. Recent work shows that retention in aMCI patients can be raised well above floor when the delay period is devoid of further material – 'Minimal Interference'. This memory enhancement is thought to be the result of improved memory consolidation. Here we used the minimal interference/interference paradigm (word list retention following 10 min of quiet resting vs. picture naming) in a group of 17 AD patients, 25 aMCI patients and 25 controls. We found (1) that retention can be improved significantly by minimal interference in patients with aMCI and patients with mild to moderate AD; (2) that the minimal interference paradigm is sensitive to decline in memory function with disease severity, even when performance on standard tests has reached floor; and (3) that this paradigm can differentiate well (80% sensitivity and 100% specificity) between aMCI patients who progress and do not progress to AD within 2 years. Our findings support the notion that the early memory dysfunction in AD is associated with an increased susceptibility to memory interference and are suggestive of a gradual decline in consolidation capacity with disease progression.

1. Introduction

The hallmark and earliest symptom of Alzheimer's Disease (AD) is severely impaired retention of new information (Albert et al., 2011; McKhann et al., 1984; Welsh, Butters, Hughes, Mohs, & Heyman, 1992). Clinically this anterograde amnesia is manifested in tests requiring the delayed recall of new material following an interval filled with further material. Performance on such tests declines steadily in the asymptomatic stages of the disease (Frisoni, Fox, Jack, Scheltens, & Thompson, 2010) and typically reaches floor or near-to-floor levels early in the symptomatic, amnestic Mild Cognitive Impairment (aMCI), stage (Cummings, Doody, & Clark, 2007; Frisoni et al., 2010; Locascio, Growdon, & Corkin, 1995; Welsh, Butters, Hughes, Mohs, & Heyman, 1991). Consequentially, delayed recall is moderately sensitive to the early memory impairment seen in aMCI but is a poor marker of disease severity and further progression (Frisoni et al., 2010; Locascio et al., 1995; Spinnler & Della Sala, 1988).

Even though these tests of delayed recall indicate maximal levels of memory impairment early in the disease, there is strong evidence from neuropathological investigations that the memory system continues to deteriorate somewhat with disease progression (Bobinski et al., 1995; Braak & Braak, 1991, 1995; Frisoni et al., 2010; Markesbery, 2010; Rössler, Zarski, Bohl, & Ohm, 2002). The asymptomatic and aMCI stages of the disease are characterised by isolated medial temporal lobe (MTL) pathology, starting in the transentorhinal region and gradually spreading to the entorhinal region as well as the hippocampus (Braak & Braak, 1991, 1995), and this pathology intensifies with AD disease progression (Bobinski et al., 1995; Braak & Braak, 1991, 1995; Frisoni et al., 2010; Markesbery, 2010; Rössler et al., 2002). If the progressive deterioration of these structures affects their cognitive counterpart, i.e. memory function, then one would predict such cognitive memory deterioration to be revealed in a test that is unburdened by early floor effects.

We have recently identified a 'Minimal Interference' delayed recall paradigm, in which retention can be raised well above floor in many amnesic patients, including those with aMCI (Cowan, Beschin, & Della Sala, 2004; Della Sala, Cowan, Beschin, & Perini, 2005; Dewar, Della Sala, Beschin, & Cowan, 2010; Dewar, Fernández García, Cowan, & Della Sala, 2009). This paradigm mirrors

* Corresponding author. Address: Human Cognitive Neuroscience, Psychology, University of Edinburgh, 7 George Square, Edinburgh EH8 9JZ, UK.
E-mail address: m.dewar@ed.ac.uk (M. Dewar).

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doi:10.1016/j.bandc.2011.12.005

the standard clinical delayed recall paradigm with one crucial exception: rather than being engaged in various cognitive tests (interference) between the learning and recall phases, the patient rests quietly in a darkened testing room during this delay so as to minimise further external cognitive stimulation. The improvement in retention that ensues is not negligible – on average aMCI patients have shown to go from around 10% retention in the interference condition to around 55% retention in the minimal interference condition, with some individuals showing somewhat larger improvements in retention (i.e. 0–100%; Della Sala et al., 2005; Dewar et al., 2009).

Minimal interference appears to improve retention in aMCI patients by allowing spared consolidation processes to function better (Dewar et al., 2009). Memory consolidation is the process during which new memory traces become strengthened over time. In neurologically intact animals this consolidation process can be disrupted by toxins, drugs and seizures, resulting in poor anterograde memory (Dudai, 2004). This disruptive effect is especially detrimental when the interference occurs immediately following learning, i.e. when the new memory trace is still weak and in need of strengthening (Dudai, 2004). The later such interference occurs, the smaller the disruptive effect, since the trace can gain in strength prior to the disruption of the consolidation process. Our recent behavioural study on memory interference, which was based on the same paradigm first used in animals, demonstrated a strikingly similar temporal gradient of post-learning *cognitive* interference in aMCI patients (Dewar et al., 2009): 12 aMCI patients were presented with lists of words, which they had to recall immediately afterwards as well as following a 9-min delay. The critical manipulation in this study was the temporal position of a 3-min picture naming task (interference) within the otherwise unfilled delay: Interference either occurred in the first (early interference), in the middle (mid interference) or in the last (late interference) portion of the delay. The patients' retention was significantly higher when the interference task occurred at the end of the delay (48%) than when it occurred at the beginning of the delay (10%), and this effect was observed in all 12 patients. Moreover, retention was also significantly higher when interference occurred at the end of the delay than when interference occurred in the middle (20%) of the delay. This substantial memory improvement via delayed interference cannot be accounted for by mere maintenance of the memoranda within working memory during the unfilled period. The picture naming task diverted the participants' attention and required overt articulation, thus acting as a rehearsal-blocker. Items in working memory are lost within seconds in the absence of continuous rehearsal (Baddeley, 1986; Baddeley & Hitch, 1974). Therefore, if minimal interference merely allowed for rote-rehearsal within working memory, without any long-term memory processing, new material should have been lost as soon as the unfilled delay was followed by the 3-min rehearsal-blocking interference, irrespective of the duration of rehearsal and the temporal position of the interference. In other words, no temporal gradient of interference would be predicted by the working memory rehearsal account.

The observed temporal gradient of interference is therefore highly indicative of a partially spared memory consolidation process in aMCI patients. The data demonstrate that these patients have some capacity to consolidate new information but that this process is disrupted severely by immediate post-learning material, resulting in an early floor effect on standard tests of delayed recall. The findings suggest that minimal interference could provide a more sensitive measure of consolidation capacity in such patients. Given the evidence for progressive deterioration of the MTL in AD (Bobinski et al., 1995; Braak & Braak, 1991, 1995; Frisoni et al., 2010; Markesbery, 2010; Rössler et al., 2002), we predict that the capacity to consolidate new material should decline with progression of disease, and that this change in memory function should be seen via our minimal interference paradigm. That is, we predict the magnitude of retention in the minimal interference condition to be in the following order: Controls > aMCI > AD. How rapidly the aMCI-to-AD decline might occur remains to be established. Indeed, we do not know whether retention can be improved in patients with AD.

Observations in previous aMCI studies indicate individual variations in retention, even at the aMCI stage, and even in patients scoring 0% following the interference delay (Della Sala et al., 2005; Dewar et al., 2009). Given that 70–100% of autopsied aMCI cases have early AD pathology (Markesbery, 2010) it is possible that these early variations in retention could reflect early differences in memory consolidation capacity and thus disease severity. If so, there is the possibility that retention in the minimal interference condition in aMCI could be predictive of progression from aMCI to AD within a given period.

We thus had three main aims in the present cross-sectional and longitudinal study:

(1) We sought to establish whether minimal interference enhances memory across the AD spectrum, including both aMCI patients and patients with mild to moderate AD.
(2) We wanted to examine whether magnitude of retention was associated with disease severity, as assessed via a continuous measure.
(3) By following up the patients longitudinally, we sought to establish how well baseline minimal interference performance level could differentiate between those aMCI patients progressing to AD and those patients who remained stable over the course of the 2-year study period.

Importantly, these longitudinal data also permitted us to examine the effects of disease severity upon retention in the minimal interference condition on a within-subjects basis, free of the potential confounds (i.e. differences in past occupation, lifestyle factors) or aetiological heterogeneity that can hamper cross-sectional designs. In other words, we were able to examine how well longitudinal within-subjects changes in retention in the minimal interference condition mapped onto within-subjects changes in disease severity. Moreover, we were able to test a group of aMCI patients who progressed to AD, and thus had (retrospectively) clinically confirmed prodromal AD at baseline. Doing so allowed for a powerful aMCI vs. AD comparison *within subjects*.

2. Materials and methods

The study consisted of three phases: Phase 1 (baseline), Phase 2 and Phase 3. Each phase was separated by 1 year (see Fig. 1).

2.1. Phase 1 (baseline)

2.1.1. Participants

Twenty-five patients with aMCI, 25 patients with mild to moderate AD (MMSE > 15) and 25 controls entered the study in Phase 1. Eight of the AD patients had to be excluded from the study as they could not be matched for education with the controls or aMCI patients. The remaining study participants in the three groups were matched for age and education (see Table 1).

The clinical diagnosis of AD was made according to the DSM-III-R criteria and the NINCDS–ADRDA criteria (McKhann et al., 1984).

The aMCI patients were diagnosed with aMCI according to Petersen et al.'s (1999) operational criteria, modified by Winblad et al. (2004) (see also Petersen et al., 2009):

(a) a memory complaint corroborated by an informant,
(b) objective memory impairment,
(c) otherwise normal general cognitive function,
(d) intact activities of daily living, and
(e) an absence of dementia.

Consistent with these criteria, all aMCI patients included in this study performed very poorly on tests of Long Term Memory (LTM). Specifically, patients scored more than 1.5 SD below the performance of healthy people on a test of delayed word list recall (Rey Auditory Verbal Learning Test) and delayed figure recall (Rey-Osterrieth Complex Figure Test). However, patient performance was within 1.5 SD of the performance of healthy people on other neuropsychological tests assessing verbal short term memory function (digit span), executive function (Trail Making Test; Verbal Fluency), language function (Verbal Fluency), visuo-spatial function (Figure Copy), and reasoning (Raven's matrices) (see Table 1). Moreover, all aMCI patients scored $\geqslant$24/30 on the Mini-Mental State Examination (MMSE), and they had a Clinical Dementia Rating score of 0.5 and an activities of daily living (ADL) score of 6.

All aMCI and AD patients had a normal neurological examination, and the controls were healthy as evinced by a normal medical history.

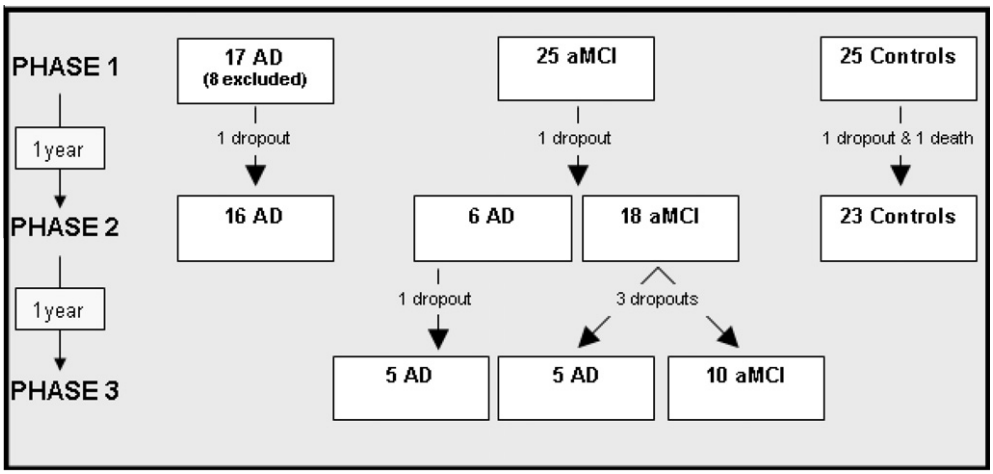

Fig. 1. Number of participants in each group entering the three Study phases, which were each separated by 1 year. Six of the original aMCI patients had progressed to AD by Phase 2. By Phase 3 ten of the original aMCI patients had progressed to AD.

Table 1
Group means and SDs for selected demographic and neuropsychological measures.

	Cut-off	AD (14f/3m)		aMCI (13f/12m)		Controls (12f/13m)		Group difference *p*-value	% of patients < cut off
		Mean	SD	Mean	SD	Mean	SD		
Age		75.59	6.65	75.72	5.86	74.80	5.72	0.87	
Education		6.35	2.21	8.36	3.89	8.84	3.91	0.079	
MMSE[b]	<24	20.76	3.15	26.08	1.32	29.76	0.52	**<0.001** (*all comparisons*)	71% AD, 0% aMCI
Geriatric depression scale[c]	>9	2.88	3.82	2.96	3.12			0.943	12% AD, 0% aMCI
Hachinski ischemic scale[d]	>4	0.71	0.99	1.16	1.03			0.161	0% AD, 0% aMCI
Global deterioation score[e]	>1	5.12	0.86	3.12	0.73			**<0.001**	All patients
Clinical dementia rating (CDR)[f]	>0	1.65	0.49	0.50				**<0.001**	All patients
Activities of daily living (ADL)[g]	<6	5.94	0.24	6.00	0.00			0.23	0.1% AD
Word list learning – total immediate[h]	<28.53[a]	30.30	6.99	30.71	5.03			0.827	29% AD, 24% aMCI
Word list delayed recall[h]	<4.69[a]	0.30	1.01	1.75	1.92			**<0.01**	All patients
Rey figure delayed recall[i]	<9.46[a]	3.69	4.54	7.05	3.27			**<0.01**	88% AD, 76% aMCI
Digit span[j]	<3.5[a]	4.83	0.90	5.13	0.68			0.218	No patients
Trail making B–A[k]	>187[a]	128.87	71.66	46.77	30.1			**<0.001**	12% AD, 0 aMCI
Phonological fluency[h]	<17.35[a]	21.44	6.00	28.72	7.99			**<0.01**	24% AD, 0 aMCI
Semantic fluency[l]	<7.25[a]	10.00	2.85	10.05	1.90			0.946	18% AD, 0 aMCI
Rey figure copy[i]	<28.87[a]	27.70	6.26	31.50	1.86			**<0.01**	41% AD, 0 aMCI
Raven's matrices[m]	<18[a]	18.35	3.04	24.40	4.04			**<0.001**	41% AD, 0 aMCI

[a] Cut off inferential 5th centile of the normal population Bold *p*-values = significant group differences.
[b] Folstein et al. (1975).
[c] Yesavage et al. (1983).
[d] Hachinski et al. (1975).
[e] Reisberg et al. (1982).
[f] Hughes, Berg, Danziger, Coben, and Martin (1982).
[g] Katz, Ford, Moskowitz, Jackson, and Jaffe (1963).
[h] Carlesimo, Caltagirone, and Gainotti (1996).
[i] Caffarra, Vezzadini, Dieci, Zonato, and Venneri (2002).
[j] Orsini et al. (1987).
[k] Giovagnoli et al. (1996).
[l] Spinnler and Tognoni (1987).
[m] Basso, Capitani, and Laiacona (1987).

2.1.2. Procedure

All participants underwent four trials, in each of which they were presented with a new word list consisting of 15 standardised words (De Mauro T., 2000). The digitally recorded word lists were presented to the participants aurally via headphones at a rate of one word every 2 s using e-prime (Psychology Software Tools, Inc.). Participants were instructed to try and remember as many of the words as possible as they would be asked to repeat them back immediately after list presentation, in any order (immediate recall). Ten minutes following the end of immediate recall all participants were asked to recall as many of the words as possible, in any order (delayed recall). No warning was given regarding the delayed recall test. It should be noted however that while delayed recall was likely to have come as a surprise in the first trial participants might have expected delayed recall during later trials. The critical manipulation occurred during the 10- min delay interval, during which participants either engaged in a picture naming task – '*interference condition*', or rested alone in the darkened testing room – '*minimal interference condition*'.

2.1.2.1. Minimal interference condition. Following immediate recall the experimenter informed the participants that she would be leaving the testing room for several minutes in order to set-up the next task, and that she would dim the lights. Participants were instructed to sit back and rest until the return of the experimenter. The experimenter subsequently left the room, returning 10 min later.

2.1.2.2. Interference condition – picture naming. The interference task was a variation on a task that has been shown to disrupt memory consolidation in aMCI patients with little effect on retrieval (Dewar et al., 2009). Following immediate recall, participants attended to a laptop monitor that visually presented a sequence of greyscale drawings of animals and everyday objects (Snodgrass & Vanderwart, 1980) via e-prime (Psychology Software Tools, Inc.). Each of the 86 pictures was presented for 3 s. The inter stimulus interval (a white screen) was either 1 s, 3 s, 5 s or 7 s, and was varied randomly throughout the task in order to keep participants focused (i.e. so that they would not become used to a set presentation rhythm). Participants were asked to focus on the screen and to name verbally the drawings presented on the screen as fast as possible.

Prior to the experiment, participants underwent a series of practise trials of the picture naming task in order to ensure that they understood and mastered the task, and to minimise the need for lengthy, potentially interfering instructions during the experiment itself. Instructions for the interference and minimal interference delays during the experiment itself could thus be equated in terms of number of words used.

2.1.3. Counterbalancing

Each participant received two trials in the minimal interference condition and two trials in the interference condition. Half of the participants in each group received the four trials in the following order: '*Minimal Interference – Interference – Minimal Interference – Interference*' (condition order 1). The other half received the four trials in the opposite order: '*Interference- Minimal Interference – Interference – Minimal Interference*' (condition order 2).

Word lists were counterbalanced in a Latin square design (1-2-3-4, 2-3-4-1, 3-4-1-2, and 4-1-2-3).

The trials were separated by brief gaps (~1 min) consisting of informal conversation.

2.1.4. Measures of disease severity

In order to obtain estimates of disease severity we assessed all patients using the Mini-Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975) and the Global Deterioration Scale (GDS) (Reisberg, Ferris, de Leon, & Crook, 1982). The GDS has seven stages and is based on both cognitive and functional factors. The stages are as following: 1 – No cognitive decline (normal); 2 – very mild cognitive decline (forgetfulness); 3 – mild cognitive decline (early confusional); 4 – moderate cognitive decline (late confusional); 5 – moderately severe cognitive decline (early dementia); 6 – severe cognitive decline (moderate dementia); 7 – very severe cognitive decline (advanced dementia).

2.2. Phase 2 (1 year post-baseline)

In Phase 2, 24 of the original aMCI patients, 16 of the original AD patients and 23 of the original controls were re-evaluated using the Phase 1 neuropsychological tests (only aMCI) and memory experiment (using the same counterbalancing order as applied in Phase 1 for each participant). Some participants were unavailable for further testing (1 aMCI, 1 AD and 1 control) and one had passed away (1 control). Moreover, 6 of the original Phase 1 aMCI patients were diagnosed with AD in Phase 2 (see Fig. 1). These patients are referred to as the Phase 1–2 aMCI-progressor group in the present paper.

2.3. Phase 3 (2 years post-baseline)

In Phase 3, 20 of the original aMCI patients were re-evaluated using the Phase 1 neuropsychological tests and memory experiment (using the same counterbalancing order as applied in Phase 1 for each participant). Four participants were unavailable for further testing (three patients diagnosed with aMCI in Phase 2 and 1 patient diagnosed with AD in Phase 2). Five of the Phase 2 aMCI patients were diagnosed with AD in Phase 3 ('Phase 2–3 aMCI-progressor group'), resulting in a total of 10 AD patients and 10 aMCI patients in Phase 3 (see Fig. 1). These patients are referred to as Phase 1–3 aMCI-progressor group and Phase 1–3 aMCI-stable group in the present paper.

2.4. Memory performance scoring

As in our previous work (Cowan et al., 2004; Della Sala et al., 2005; Dewar et al., 2009, 2010) a percentage retention score was computed for each participant for each of the 4 trials by dividing the number of correct words recalled at delayed recall by the number of correct words recalled at immediate recall in the same trial, and multiplying this score by 100. Such procedure controls for potential individual and group differences as well as any intertrial variation at immediate recall. A mean minimal interference percentage retention score was computed for each participant by averaging his/her percentage retention scores in the two minimal interference trials. A mean interference percentage score was computed for each participant via the same procedure. This procedure was justified since the two percentage retention scores per condition did not differ significantly in either group (all $p > 0.05$).

Mean absolute percentage scores, i.e. number of words recalled out of 15, were also computed for the two conditions.

'Phase 1 to Phase 2 change' scores and 'Phase 1 to Phase 3 change' scores were computed by subtracting Phase 2 scores from Phase 1 scores and Phase 3 scores from Phase 1 scores respectively.

2.5. Data analysis

Mixed factors ANOVAs were run to examine the effect of Delay condition (Minimal Interference vs. Interference) and Group (AD vs. aMCI vs. Controls) on percentage retention. Planned post-hoc comparisons were carried out using the Newman Keuls test and ANOVAs. Pearson correlations were run to examine potential asso-

ciations between retention and disease severity (MMSE scores and the GDS scores).

A receiver operating characteristic (ROC) curve analysis (Zweig & Campbell, 1993) was conducted to examine the sensitivity (hit rate) and specificity (1 – false alarm rate) of Phase 1 minimal interference percentage retention for differentiating between the Phase 1–3 aMCI-progressor group and the Phase 1–3 aMCI-stable group.

The effects of neuropsychological test performance, interference stimuli, and proactive interference on retention were examined via ANOVAs and Pearson correlations.

The alpha level was set to 0.05 for all analyses, which were conducted using SPSS 17.

The study was approved by the local Ethical Committee, and informed consent was obtained from each participant according to the Declaration of Helsinki.

3. Results

We first report the cross-sectional data (Phase 1), which were collected in order to examine whether memory is enhanced in patients across the AD spectrum under conditions of minimal interference, and whether disease severity affects retention level under such conditions. We then report the longitudinal data, which were gathered to examine potential *within subjects* associations between changes in disease severity and changes in retention in the minimal interference condition. Lastly, we present the analyses conducted in order to examine how well the Phase 1–3 aMCI stable group and the Phase 1–3 aMCI progressor group could be differentiated based on their initial Phase 1 retention scores in the minimal interference condition.

3.1. Cross-sectional – Phase 1

3.1.1. aMCI vs. AD

Fig. 2 shows that all groups, including the AD group, benefitted substantially from minimal interference according to the percentage retention scores (Delay Condition effect) [$F(1,64) = 119.975$, $p < 0.001$, $\eta_p^2 = 0.652$]. This benefit was significantly larger in the aMCI group than the AD group (Delay Condition × Group interaction, only patients included) [$F(1,40) = 10.576$, $p < 0.01$, $\eta_p^2 = 0.209$]. Indeed, while the two patient groups did not differ significantly following the interference delay [$F(1,41) = 0.670$, $p = 0.418$, $\eta_p^2 = 0.016$], the aMCI group significantly outperformed the AD group following the minimal interference delay [$F(1,41) = 12.636$, $p < 0.005$, $\eta_p^2 = 0.240$]. These results remained the same even when those aMCI patients and AD patients scoring zero in both conditions were removed from the dataset (3/25 aMCI patients and 3/17 AD patients). The findings also remained robust when the absolute delayed recall percentage scores were considered (see absolute scores in Table 2).

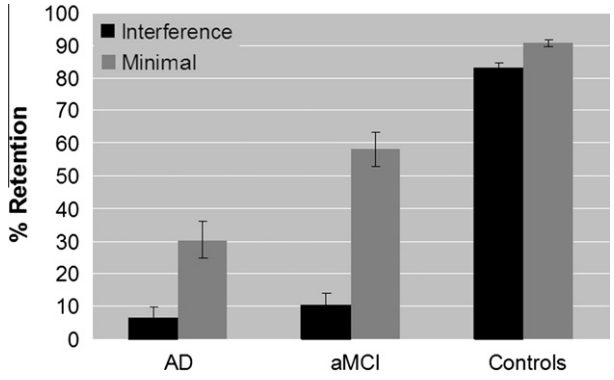

Fig. 2. Percentage word list retention in the AD, aMCI and control groups in Phase 1 following the 10 min interference (filled) delay and the 10 min minimal interference (unfilled) delay. Error bars = SEM.

Immediate recall differed significantly between the patient groups (aMCI > AD) (see Table 2). However, retention in the minimal interference condition continued to remain significantly higher in the aMCI group than the AD group even when several participants (2 AD and 8 aMCI) were excluded to allow for the retrospective matching of the two groups at immediate recall [$F(1,31) = 5.646$, $p < 0.05$], (Immediate recall difference [$F(1,31) = 0.476$, $p = 0.495$]).

Fig. 2 further demonstrates that the aMCI group and the AD group performed poorer than the healthy controls in both conditions (Group effect) ($p < 0.001$). However, the difference between patients and controls was significantly smaller in the minimal interference condition than in the interference condition (Delay Condition × Group effect) for both the AD group [$F(1,40) = 9.758$, $p < 0.01$] and the aMCI group [$F(1,48) = 61.438$, $p < 0.001$].

3.1.2. Disease severity (patients only)

Strong correlations were obtained in Phase 1 between retention level in the minimal interference condition and the MMSE ($r^2 = .315$, $p < 0.001$) (see Fig. 3) as well as the GDS ($r^2 = .276$, $p < 0.001$), thus indicating that retention in the minimal interference condition was higher in patients whose disease was less severe. These correlations stayed robust even when only including those participants whose minimal interference score was >0 (22/25 aMCI patients and 14/17 AD patients). Correlational analyses for the two groups (aMCI and AD) separately revealed a significant correlation between retention in the minimal interference condition and the MMSE in the AD group ($r^2 = .293$, $p < 0.05$). No other correlations were found to be significant in the minimal interference retention condition. Moreover, no significant correlations were obtained between retention in the interference condition and the MMSE, or between retention in interference condition and the GDS, in the patient sample as a whole, or in the two groups separately. These data indicate that retention in the minimal interference condition was considerably more sensitive to differences in disease severity than was retention in the interference condition, which was at floor.

3.2. Longitudinal

3.2.1. Phase 1 to Phase 2 change – group differences

The mean change in retention from Phase 1 to Phase 2 in the minimal interference condition did not differ significantly between the three groups, though it approximated significance ($p = 0.062$).

Since six of the 25 Phase 1 aMCI patients received an AD diagnosis at Phase 2 the above analysis was repeated with the aMCI group split into Phase 1–2 aMCI-progressor and Phase 1–2 aMCI-stable groups. This analysis revealed a significant group difference in change in retention in the minimal interference condition from Phase 1 to Phase 2 [$F(3,56) = 10.834$, $p < 0.001$, $\eta_p^2 = 0.380$] which was driven by a significantly larger retention change in the AD group (Mean = −13.56% retention, SD = 16.26) and the Phase 1–2 aMCI-progressor group (Mean = −31.79% retention, SD = 28.28) than the controls (Mean = +1.14% retention, SD = 9.98) and the Phase 1–2 aMCI-stable group (Mean = +5.73% retention, SD = 16.26). The Phase 1–2 aMCI-stable patients who progressed to AD from Phase 2 to Phase 3 (Phase 2–3 aMCI-progressor group) subsequently declined in retention in the minimal interference condition from Phase 2 to Phase 3. The magnitude of this decline (Mean = −38.61% retention, SD = 9.15) was comparable to that observed in the Phase 1–2 aMCI-progressor patients from Phase 1 to Phase 2 ($p = 0.706$). In other words, the two aMCI-progressor groups showed comparable and indeed AD-like drops in retention

Table 2
Group mean absolute percentage recall scores ((/15 words) × (100)) for immediate recall, delayed recall in the minimal interference condition and delayed recall in the interference condition in Phase 1.

	Mean immediate % Recall		Minimal delayed % Recall		Interference delayed % Recall	
	Mean	SD	Mean	SD	Mean	SD
AD	23.13	6.17	7.26	6.59	1.18	2.02
aMCI	29.21	7.24	18.67	9.23	3.20	5.22
Controls	48.50	4.93	44.27	8.02	38.67	5.53

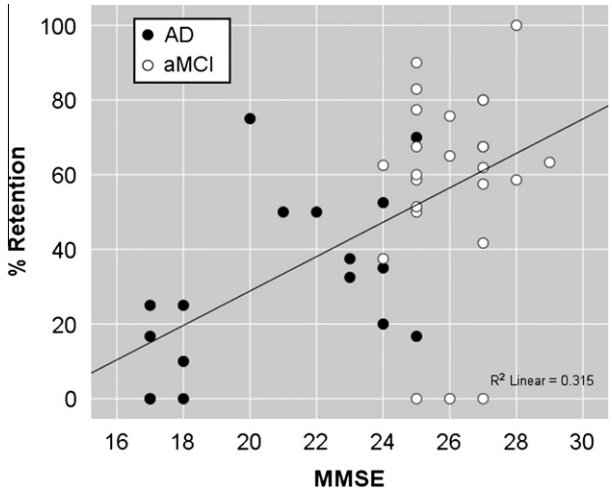

Fig. 3. Correlation between percentage word list retention in the minimal interference condition and MMSE score in Phase 1.

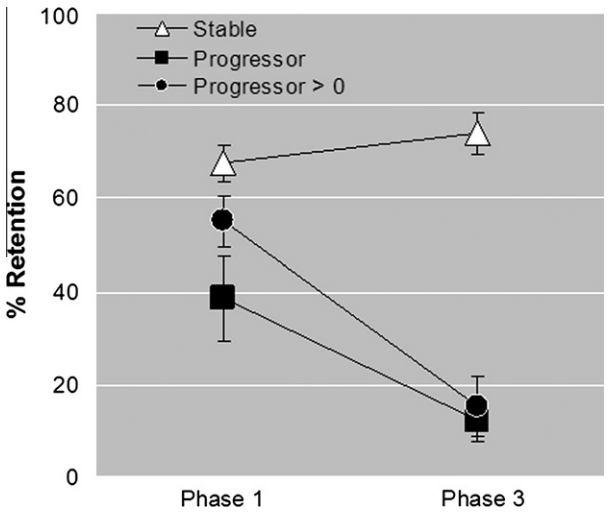

Fig. 4. Percentage retention in the minimal interference condition in Phase 1 and Phase 3 in the aMCI patients who progressed to AD from Phase 1 to Phase 3 and the aMCI patients who remained stable from Phase 1 to Phase 3. Three aMCI-progressor patients had zero retention in Phase 1. The aMCI-progressor data are thus shown including these patients (Progressor) and excluding these patients (Progressor > 0). Error bars = SEM.

in the minimal interference condition in the year preceding their AD diagnosis.

Patients scoring zero on the delayed recall test of Phase 1 were excluded from these analyses since their retention could not drop any further over time (3/25 aMCI patients and 3/17 AD patients).

There were no significant differences between the various groups in the change in immediate recall performance from Phase 1 to Phase 2 (all $p > 0.1$).

3.2.2. Phase 1 to Phase 2 change – disease severity

In the aMCI sample as a whole the magnitude of change in retention in the minimal interference condition from Phase 1 to Phase 2 correlated significantly with the magnitude of change in MMSE score ($r^2 = .201$ $p < 0.05$), but not with the magnitude of change in GDS score, though the latter approached significance ($r^2 = .141$, $p = 0.07$).

Patients scoring zero on the delayed recall test of Phase 1 were excluded from these analyses since their retention could not drop any further over time.

There was very little change in immediate recall performance from Phase 1 to 2 in the aMCI group (Mean = −1.81%, SD = 5.02), and no significant correlations were revealed between this change and change in disease severity from Phase 1 to Phase 2. Immediate recall also changed little from Phase 1 to 2 in the AD group (Mean = −4.32, SD = 5.24) and the Control group (Mean = −4.32, SD = 4.29).

3.2.3. Phase 1 to Phase 3 change – disease severity (aMCI only)

A significant correlation was obtained between the magnitude of change in retention in the minimal interference condition and the magnitude of change in GDS score from Phase 1 to Phase 3 in the aMCI group ($r^2 = .376$, $p < 0.01$). A near significant correlation was also obtained between the magnitude of change in retention in the minimal interference condition and the magnitude of change in MMSE score from Phase 1 to Phase 3 ($r^2 = .213$, $p = 0.053$). Patients scoring zero on the delayed recall test of Phase 1 were excluded from this analysis since their retention could not drop any further over time.

There was very little change in immediate recall performance from Phase 1 to 3 in the aMCI group (Mean = −3.5%), and no significant correlations were revealed between this change and the change in disease severity from Phase 1 to Phase 3.

3.2.4. Phase 1–3 aMCI-stable vs. aMCI-progressor groups – change in retention

A significant difference in the change in retention in the minimal interference condition between Phase 1 and Phase 3 was shown between those aMCI patients who remained stable and those who progressed to AD during this study (Progressor Group effect) [$F(1,16) = 26.926$, $p < 0.001$, $\eta_p^2 = 0.642$] (see Fig. 4). Whereas the aMCI-progressor patients dropped by an average of 39.61% retention ($p < 0.001$), the aMCI-stable patients' retention remained stable (+6.52% retention, $p = 0.323$). Patients scoring zero on the delayed recall test of Phase 1 were excluded from this analysis since their retention could not drop any further over time.

No group differences were found in the change from Phase 1 to Phase 3 retention in the interference condition ($p = 0.981$), which was at floor in both Phases in both groups. Moreover, the change in absolute immediate recall from Phase 1 to 3 was small in both groups (−4.33% and 2.66% for the progressor and stable group respectively) and did not differ significantly [$F(1,19) = 0.323$, $p = 0.577$].

3.2.5. Phase 1–3 aMCI-stable vs. aMCI-progressor groups – baseline performance

Repetition of the Phase 1 Group × Delay Condition ANOVA with the aMCI sample split into Phase 1–3 aMCI-progressor group and Phase 1–3 aMCI-stable group revealed that in the Phase 1 minimal interference condition the Phase 1–3 aMCI-stable group performed significantly better (Mean = 67.56% retention, SD = 12.53) than the Phase 1–3 aMCI-progressor group (Mean = 38.56% retention, SD = 29.2) (see Fig. 4) and the AD group (Mean = 30.30% retention, SD = 23.21) (Group effect, $p < 0.05$, $\eta_p^2 = 0.316$ and 0.465 respectively). The Phase 1–3 aMCI-progressor group and the AD group did not differ significantly in minimal interference retention. This was however largely due to the three aMCI-progressors who had zero retention in Phase 1 (Phase 1–3 aMCI progressor group mean without these three patients = 55.08% retention). No group differences were revealed in the Phase 1 interference condition.

The ROC curve analysis (Zweig & Campbell, 1993) was run in order to establish how well Phase 1 minimal interference retention could differentiate between the Phase 1–3 aMCI-progressor group and the Phase 1–3 aMCI-stable group. The ROC curve shown in Fig. 5 illustrates the trade-off between sensitivity (hit rate) and false alarms (1-specificity) for various retention cut-off values. As shown in the curve a Phase 1 minimal interference retention cut-off of 58.04% provided 80% sensitivity and 100% specificity for progression from aMCI to AD from Phase 1 to Phase 3. In other words, by using this cut-off value, 80% of the aMCI-progressor patients were correctly classified as belonging to the aMCI-progressor group, and all aMCI-stable patients were correctly classified as belonging to the aMCI-stable group. This cut-off resulted in a positive predictive value (PPV) of 100% and a negative predictive value (NPV) of 83.33%. The area under the curve for the minimal interference condition was significantly larger than chance (Area under the curve = 0.840, $p < 0.05$). Minimal interference retention continued to have high sensitivity (71.4%) and specificity (100%) at the 58.04% cut-off even when the three aMCI-progressors scoring zero in Phase 1 were excluded from the ROC curve analysis.

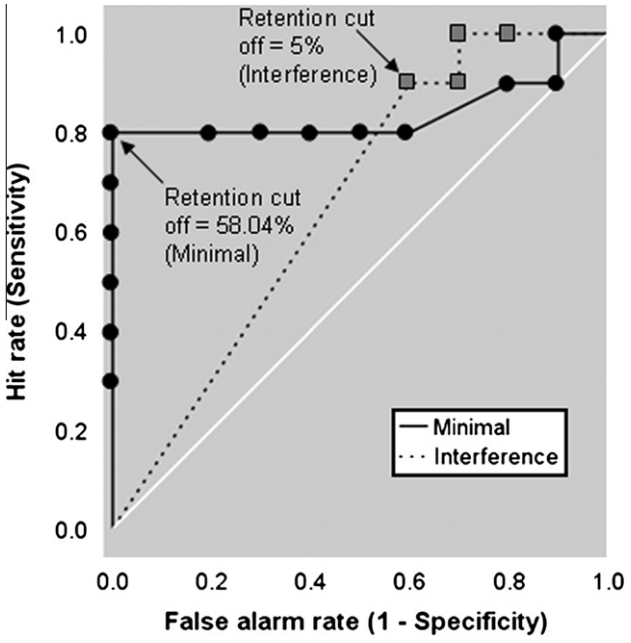

Fig. 5. ROC curve showing the hit rate (sensitivity) and the false alarm rate (1 – specificity) for Phase 1 retention cut-off values in the minimal interference condition (black line) and the interference condition (dotted line) for differentiating between the aMCI patients who did and did not progress to AD from Phase 1 to Phase 3. The white line depicts chance level. A retention cut-off of 58.04% in the minimal interference condition in Phase 1 provided 80% sensitivity and 100% specificity for progression to AD from Phase 1 to Phase 3. A retention cut-off of 5% in the interference condition in Phase 1 provided 90% sensitivity but only 40% specificity for progression to AD from Phase 1 to Phase 3.

Phase 1 interference retention on the other hand had poor classification power (90% sensitivity but only 40% specificity for a retention cut-off of 5%, Area under the curve = 0.660, $p = 0.226$, (see Fig. 5). When this ROC curve analysis was repeated with only those patients scoring >0% in the Phase 1 interference condition ($N = 5$) Phase 1 interference retention had 100% sensitivity and 75% specificity for a cut-off of 22.92% retention, though, given the small sample, the area under the curve was not significantly larger than chance (Area under the curve = 0.750, $p = 0.480$).

3.3. Further analyses

3.3.1. Minimal interference and neuropsychological test performance

No significant correlations were shown between retention in the minimal interference condition and any of the neuropsychology tests listed in Table 1 (except for the MMSE and GDS).

Moreover, there were no significant differences in performance on these tests between the Phase 1–3 aMCI-progressor group and the Phase 1–3 aMCI-stable group, or between the Phase 1–2 aMCI-progressor group and the Phase 1–2 aMCI-stable group.

3.3.2. Minimal interference performance and proactive interference

A possible build up of proactive interference was examined by checking for a decline in immediate recall performance across the four trials in Phase 1. No such decline was revealed in the participants in this study (Trial effect) [$F(3,192) = 1.536$, $p = 0.206$, $\eta_p^2 = 0.023$]. Moreover, there was no Trial by Group interaction [$F(6,192) = 0.831$, $p = 0.547$, $\eta_p^2 = 0.025$], indicating that performance across the four trials did not vary differently in the three groups. These findings held when only the patient data were examined ($p = 0.756$ and $p = 0.715$ respectively).

We also counted and examined the number of intrusions from prior word lists that were made during recall in the minimal interference condition. Doing so allowed us to examine whether the group differences in retention in the minimal interference condition were associated with potential group differences in the degree of proactive interference. The number of intrusions was very low. Two aMCI patients and four AD patients made intrusions at immediate recall, and four aMCI patients and 2 AD patients made intrusions at delayed recall. The group average number of intrusions made at immediate recall was 0.15 for the AD group and 0.12 for the aMCI group, and this difference was non-significant ($p = 0.214$, Mann–Whitney U test). The group average number of intrusions made at delayed recall was 0.06 for the AD group and 0.26 for the aMCI group, and this difference was also non-significant ($p = 0.613$, Mann–Whitney U test).

3.3.3. Trial 1 performance

Delayed recall came as a surprise in the first testing trial. It was therefore considered especially unlikely that participants would attempt to continuously rote-rehearse word list material during the minimal interference delay in this trial (see also Cowan et al., 2004; Della Sala et al., 2005; Dewar et al., 2009, 2010). The Trial 1 data were thus analysed separately in order to examine the effect of minimal interference vs. interference upon retention without potential contamination by added rote-rehearsal effects. As noted in the methods section half of the participants received minimal interference in Trial 1, while the other half received interference in Trial 1.

3.3.3.1. aMCI and AD. A one way ANOVA was run on the Trial 1 retention data, with between subjects factor Trial 1 condition (Minimal interference vs. Interference). A clear benefit of minimal

interference was revealed across the patients in Trial 1: The patients who received the minimal interference condition in Trial 1 showed significantly higher retention than did the patients who received the interference condition in Trial 1 (Trial 1 condition effect) [$F(1,41) = 32.490$, $p < 0.001$, $\eta_p^2 = 0.448$].

3.3.3.2. Disease severity. The means and ranges of the MMSE and GDS for the Trial 1 minimal interference group were very similar to those of the sample as a whole. This permitted examination of the association between disease severity and minimal interference retention in the Trial 1 Minimal interference group only. A significant correlation was revealed between retention in the minimal interference condition and the GDS in Trial 1 ($r^2 = .173$, $p < 0.05$). The correlation between retention in the minimal interference condition and the MMSE approached significance ($r^2 = .156$, $p = 0.062$).

3.3.4. Intrusions from the Interference task

The number of intrusions from the interference stimuli at delayed recall in the interference condition was low for all groups. The aMCI patients (Mean = 0.12) did not differ significantly from the Controls (Mean = 0) in the number of intrusions made ($p = 0.153$, Mann–Whitney U test). In fact, only two aMCI patients made intrusions (1 and 2 intrusions). The AD group made slightly more intrusions than the aMCI group and the Controls (Mean = 0.62, $N = 10$), and this difference was significant ($p < 0.05$, Mann–Whitney U test). However, there was no significant correlation between number of these intrusions and retention in the minimal interference condition in the AD group.

4. Discussion

There were three principal findings in our study: Firstly, retention could be enhanced via minimal interference in the majority of patients ranging from aMCI to mild to moderate AD (Fig. 2). Secondly, retention in the minimal interference condition was associated with disease severity, with greater disease severity leading to reduced levels of retention (Figs. 2 and 3). No such association was revealed between retention in the interference condition and disease severity. Thirdly, the magnitude of retention in the minimal interference condition at baseline was a strong predictor of progression from aMCI to AD (Figs. 4 and 5). These findings and their implications will be discussed in detail below.

4.1. Memory improvement across the AD spectrum

The finding that the majority of aMCI and AD patients showed enhanced retention following an unfilled delay interval demonstrates that *both* aMCI and AD patients have a capacity to retain new material over delays, provided that such delays are free of further material. The aMCI findings are in line with previous reports of memory enhancement via minimal interference in smaller samples of aMCI patients (Della Sala et al., 2005; Dewar et al., 2009) and, as such, lend stronger credence to this phenomenon in aMCI. The AD findings are novel in that they reveal that this phenomenon is not specific to the aMCI stage of AD, and indeed that some capacity to retain new material under these conditions is preserved as AD progresses to its mild to moderate forms.

In line with the prior work on minimal interference and memory consolidation (Dewar et al., 2009) we hypothesise that the improved retention observed here is associated with spared memory consolidation capacity in both aMCI and AD. Indeed, as in our earlier work on aMCI (Dewar et al., 2009), there was little support for potential alternative accounts of the patients' improved retention, i.e. 'reduced retrieval competition' and 'rehearsal within working memory'.

Retrieval competition was expected to be low in both the minimal interference condition and the interference condition, given that it is dependent upon a high similarity between the memoranda and interpolated stimuli (Anderson & Bjork, 1994; McGeoch & Nolen, 1933; Mensink & Raaijmakers, 1988; see also Wixted, 2004). The very low number of intrusions from pictures at delayed recall suggests that retrieval competition was indeed minimal, as was also concluded in the earlier work on aMCI using a picture naming task (Dewar et al., 2009). The data thus suggest that the interference observed here occurred during consolidation rather than during retrieval, and therefore that retention was improved via minimal interference as a result of reduced interference during consolidation.

There is the possibility that minimal interference could have allowed for superior consolidation of the words by providing an opportunity for patients *to intentionally rehearse* the words within long term memory (i.e. elaborative rehearsal) rather than simply allowing an *automatic* consolidation process to work better. We have already demonstrated successfully in both aMCI patients and patients with amnesia due to traumatic brain injury that memory improvement can occur in the absence of continuous rote-rehearsal, indicating that the minimal interference effect is not simply associated with maintenance of new material within working memory (Cowan et al., 2004; Della Sala et al., 2005; Dewar et al., 2009, 2010). The present Trial 1 data indicate that the memory improvement can also occur in the absence of sporadic intentional rehearsal within long term memory. No forewarning was provided regarding delayed recall. Therefore, the probability of either type of rehearsal was expected to be minimal, at least in the first trial. If the memory improvement observed had merely been the result of rehearsal, retention should have been at floor on Trial 1, irrespective of delay condition. However, patients receiving the minimal interference condition in Trial 1 significantly outperformed the patients receiving the interference condition in Trial 1. Of course we cannot rule out the possibility that some participants might have attempted to rehearse during the unfilled delays in Trials 2–4. However, the evidence above suggests that any such rehearsal is unlikely to have contributed substantially to the minimal interference effects revealed in this study. Indeed, the Trial 1 data suggest that memory consolidation can be improved in aMCI and AD patients by mere wakeful resting, without any added intentional rehearsal. We propose a cognitive account of this consolidation effect at the end of the discussion.

4.2. Higher retention in aMCI than AD in the minimal interference condition

In line with our hypothesis, retention in the minimal interference condition was higher in the aMCI group than the AD group, thus indicating that the capacity to retain new material under conditions of minimal interference drops with progression from aMCI to AD.

This group difference cannot be explained by potentially different 'premorbid' performance levels associated with uncontrolled variables, such as lifestyle factors or previous occupation. We avoided such shortcomings a priori by following up our patients longitudinally. This allowed for a within-subjects comparison of retention in the minimal interference condition in the aMCI-progressor patients during the aMCI stage *and* the AD stage. These data were wholly in accordance with our cross-sectional data, in that retention in the minimal interference condition was significantly lower during the AD stage than during the aMCI stage (see Fig. 4). Indeed, all 7 aMCI-progressor patients who showed any retention in the minimal interference condition during the aMCI stage performed poorer in Phase 3 minimal interference than in Phase 1 minimal interference. This contrasted with the aMCI pa-

tients who remained stable over the 2 years and who did not show any significant drop in retention in the minimal interference condition from Phase 1 to Phase 3.

Importantly, the longitudinal data further verified that the retention differences between aMCI and AD under conditions of minimal interference could not simply be accounted for by potential aetiological heterogeneity in the aMCI sample. Since clinical confirmation of AD was available for the aMCI-progressor patients it could be ascertained retrospectively that their aMCI symptoms were indeed the result of early AD, and thus that their decline in retention in the minimal interference condition was associated entirely with progression of AD. The rate of this decline in the aMCI-progressor patients was especially pronounced and indeed AD-like in the year prior to AD diagnosis, suggesting that memory performance declines rapidly with progression to AD.

The finding of a difference between the aMCI and the AD groups in retention in the minimal interference condition is of considerable interest given that retention in the interference condition was at floor in both patient groups, in the between subjects and within subjects analysis (see Fig. 2). The early floor effect, which is well known in the field (see for example Cummings et al., 2007; Frisoni et al., 2010; Locascio et al., 1995; Welsh et al., 1991, 1992), has complicated attempts to examine differences in memory performance in aMCI and AD patients. The present study shows that this is not the case when minimal interference is utilised. Indeed, our minimal interference paradigm provided a novel window into the apparent differences in memory performance between aMCI and AD.

By definition aMCI and AD patients differ in various cognitive domains, thus raising the possibility that dysfunction in non-memory domains, e.g. executive dysfunction, could have produced the group difference in memory performance. However, the lack of significant correlations between the scores of the neuropsychological battery and retention in the minimal interference condition render this hypothesis unlikely. Moreover, even though the aMCI-stable and aMCI-progressor patients differed significantly in retention in the minimal interference condition at baseline, they did not differ significantly in performance on the neuropsychological battery at baseline.

The AD group made slightly more picture intrusions in the interference condition than did the aMCI group, thus hinting at the presence of subtle source monitoring or retrieval deficits. However, any such deficits are unlikely to have had major effects upon retention in the minimal interference condition, insofar as no correlation was observed between retention in the minimal interference condition and these intrusions. The low proactive interference from list words, and indeed lack of a group difference in such proactive interference, adds to this finding, indicating that the differences in retention in the minimal interference condition in the present patients cannot be explained away by potential memory difficulties associated with executive dysfunction. We note that this conclusion cannot be generalised to the severe stages of AD, in which any spared memory capacity would be likely to be hindered by major and widespread cognitive and behavioural impairment.

In the present patients ranging from aMCI to moderate AD however, it appears that the minimal interference paradigm taps into consolidation capacity and consolidation capacity differences between aMCI and AD patients.

4.3. Correlation between retention in the minimal interference condition and disease severity

Retention in the minimal interference condition not only differed between the dichotomised severity groups, i.e. aMCI vs. AD, but also correlated with continuous measures of disease severity. Thus, whereas retention in the interference condition did not vary significantly between severity groups in Phase 1, retention in the minimal interference condition was strongly correlated with MMSE (see Fig. 3) and GDS scores in Phase 1. This finding was substantiated by the longitudinal aMCI data showing that aMCI patients whose disease severity increased over time showed a reduction in retention in the minimal interference condition. aMCI patients whose disease severity level did not increase (substantially) on the other hand retained a stable effect of minimal interference.

As is evident from Fig. 3 the correlation between retention in the minimal interference condition and disease severity was not simply the result of the difference in retention in the aMCI and AD groups. In other words, retention scores were not merely scattered tightly within two distinct groups. The finding that the correlation between retention in the minimal interference condition and disease severity remained significant even when only AD patients were considered indicates that retention in the minimal interference condition continues to decline with increasing disease severity, even after a diagnosis of AD is made.

It is important to note that even though the association between retention in the minimal interference condition and disease severity was fairly robust across our sample it did not hold for all patients. Three of the patients scoring 0 in the minimal interference condition in Phase 1 had relatively high MMSE scores (25, 26 and 27). In contrast, one of the patients scoring in the lower range of the MMSE (20) had high retention in the minimal interference condition (75%). This finding suggests that memory function does not decrease with disease severity in a uniform manner across all patients. This hypothesis is in accordance with recent work showing that the extent of damage to the various cognitive systems as well as the order in which these systems are affected during the course of AD is not homogeneous (Davidson et al., 2010; Snowden et al., 2007; Stopford, Snowden, Thompson, & Neary, 2007, 2008).

Similarly, the absence of a significant correlation in the aMCI patients' baseline data is not surprising given the small range in cross-sectional MMSE scores (29–25) that define this group. While able to pick up the early floor effect in memory in these patients, the MMSE is unlikely to be able to pick up the subtle differences in memory function that are apparent in the minimal interference paradigm.

4.4. Predictor of progression from aMCI to AD

These early differences in memory function in the minimal interference paradigm appear to be rather telling with respect to progression from aMCI to AD. Indeed, the re-analysis of the Phase 1 data with the aMCI patients split into Phase 1–3 aMCI-stable and Phase 1–3 aMCI-progressor groups revealed that these two groups differed significantly in *baseline* (Phase 1) minimal interference retention, with the stable group retaining more verbal material than did the progressor group (see Fig. 4). In fact, as demonstrated by Fig. 5 the magnitude of baseline retention in the minimal interference condition was found to be a strong predictor of progression from aMCI to AD from baseline to Phase 3 (i.e. over 2 years) in our sample (80% sensitivity and 100% specificity). No strong prediction could be made on the basis of standard filled delay retention scores, which were very low in both the aMCI-stable and the aMCI-progressor groups. Indeed, 15 out of these 20 aMCI patients followed up until Phase 3 had 0% retention in the interference condition in Phase 1. Out of the five patients who scored >0% in the interference condition four remained stable and one progressed to AD (interference retention = 12.5%). This Phase 1–3 aMCI-progressor patient had the lowest minimal interference retention score out of these five patients. These sample numbers are too

low to permit firm conclusions to be drawn, and more extensive work is of course needed if these findings are to be implicated clinically. Nonetheless, the data hint that patients who are able to retain some material (more than 23%) in the present interference condition are unlikely to progress to AD within 2 years. This is likely to reflect earlier stages of disease and thus more consolidation capacity. In such cases minimal interference might not add very much information regarding prognosis. However, as interference retention scores approach floor, the minimal interference paradigm appears to be somewhat useful regarding prognosis over a 2-year period. Indeed, given the high frequency of eventual progression from aMCI to AD (Morris, 2006; Morris et al., 2001; Petersen, 2004) it appears likely that those aMCI patients with low retention in the minimal interference condition at baseline were already more advanced in disease progression and thus closer to a full blown AD diagnosis than were the aMCI patients with relatively high retention in the minimal interference condition.

4.5. Consolidation deficit and spared capacity in aMCI and AD – a cognitive proposal and implications

The present findings support the theory that the early memory dysfunction in AD is characterised by a heightened susceptibility to post-learning interference and demonstrate that retention can be much improved by removal of such interference in aMCI patients and patients with mild to moderate AD. This capacity to remember under conditions of minimal interference wanes gradually as the disease progresses from aMCI to its mild to moderate stages, even when 'maximum' memory impairment has been reached in the standard interference delayed recall paradigm. This waning of retention in the minimal interference paradigm is not only indicative of disease severity per se but also of imminent progression from aMCI to AD.

The early susceptibility to post-learning material appears to be brought about by an early malfunction of the consolidation system (Dewar et al., 2009, 2010). The exact nature of this malfunction remains unknown. It could be associated with a reduction in consolidation capacity (i.e. neuronal/synaptic loss within the hippocampus), and thus with insufficient capacity for the consolidation of to-be-retained material *and* post-learning material. This capacity reduction could result in resource competition, inadequate consolidation and hence poor retention when post-learning material is present. If so, minimal interference would be expected to lead to a sufficient degree of consolidation and thus retention by allowing residual resources to be focused upon the to-be-retained material. An alternative view is that the early malfunction of the consolidation system is associated with a breakdown of a 'gatekeeper'. In the healthy brain such gatekeeper might protect the consolidation system from information overload. In keeping with this hypothesis it has been suggested recently that the rhinal cortex, which is affected very early in the course of AD (Braak & Braak, 1991, 1995), might contribute to memory consolidation by transiently holding onto new multi-sensory information and selectively gating entry into the hippocampus (Fernández & Tendolkar, 2006; Iijima et al., 1996). Damage to such a gatekeeper could result in information overload and the 'crashing' of the consolidation process when post-learning material is present. If so, minimal interference might act as an 'artificial gatekeeper' by limiting the amount of information entering the consolidation system, i.e. the hippocampus. In both cognitive accounts the amount of retention under conditions of minimal interference would depend upon the 'residual retention' capacity, i.e. the capacity to consolidate new information under these conditions. It is the *level* of this residual retention capacity that could be indicative of further spread and thus of imminent progression from aMCI to AD.

Independent of which of these two cognitive accounts turn out to best explain the data reported here our findings highlight several important issues relating to the assessment of memory and cognition. While cognitive tests run in succession tend to be treated as separate tasks with a well-defined start and end, such does not necessarily translate to the underlying neural activity. A learning task is 'completed' after immediate recall, yet the memoranda are consolidated subsequently in an offline manner while one engages in new activities and tasks (c.f. Peigneux et al., 2006). Such concurrent activity can result in memory interference, especially in amnesic patients. As demonstrated by our current and previous findings, 'filler' tasks do not simply fill the time between learning and delayed recall but in fact can contribute actively to poor delayed recall by interfering with memory consolidation. In doing so, filler tasks can hamper assessment of the degree of memory impairment and of changes in memory impairment over time. As revealed here, this is not the case when a minimal interference delay is used. The present findings also indicate that differences in filler activity could lead to undue variations in memory test performance across research studies and clinical assessment. A patient asked to sit in the waiting room in between learning and delayed recall is likely to present with less severe amnesia than a patient asked to undergo extensive neuropsychological testing in between learning and delayed recall. Any such variations across follow-ups could blur true changes in memory impairment over time, highlighting the need to apply a standardised filler task – preferably minimal interference. Lastly, given the substantial improvements in retention via minimal interference, wakeful resting could provide a valuable tool for boosting memory in patients with aMCI and mild to moderate AD.

Acknowledgments

We would like to thank Alzheimer's Research UK for funding this study (Postdoctoral Research Fellowship to M.D.) and the Royal Society of Edinburgh/Lloyds TSB Foundation for Scotland who are currently providing M.D.'s salary.

We are extremely grateful to all of the patients and controls who volunteered to take part in this study and to three anonymous reviewers who provided very helpful comments on this manuscript.

References

Albert, M. S., DeKosky, S. T., Dickson, D., Dubois, B., Feldman, H. H., Fox, N. C., et al. (2011). The diagnosis of mild cognitive impairment due to Alzheimer's Disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's Disease. *Alzheimer's & Dementia, 7*, 270–279.

Anderson, M., & Bjork, R. (1994). Mechanisms of inhibition in long-term memory: A new taxonomy. In D. Dagenbach & T. Carrn (Eds.), *Inhibitory processes in attention, memory and language* (pp. 265–326). New York: Academic Press.

Baddeley, A. (1986). *Working memory*. Oxford: Clarendon Press.

Baddeley, A., & Hitch, G. (1974). Working memory. In G. Bower (Ed.), *The psychology of learning and motivation* (pp. 47–89). New York: Academic Press.

Basso, A., Capitani, E., & Laiacona, M. (1987). Raven's coloured progressive matrices: Normative values on 305 adult normal controls. *Functional Neurology, 2*, 189–194.

Bobinski, M., Wegiel, J., Wisniewski, H. M., Tarnawski, M., Mlodzik, B., Reisberg, B., et al. (1995). Atrophy of hippocampal formation subdivisions correlates with stage and duration of Alzheimer Disease. *Dementia and Geriatric Cognitive Disorders, 6*, 205–210.

Braak, H., & Braak, E. (1991). Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathologica, 82*, 239–259.

Braak, H., & Braak, E. (1995). Staging of Alzheimer's Disease-related neurofibrillary changes. *Neurobiology of Aging, 16*, 271–278.

Caffarra, P., Vezzadini, G., Dieci, F., Zonato, F., & Venneri, A. (2002). Rey-Osterrieth complex figure: Normative values in an Italian population sample. *Neurological Sciences, 22*, 443–447.

Carlesimo, G. A., Caltagirone, C., & Gainotti, G. (1996). The Mental Deterioration Battery: Normative data, diagnostic reliability and qualitative analyses of

cognitive impairment. The Group for the Standardization of the Mental Deterioration Battery. *European Neurology, 36*, 378–384.
Cowan, N., Beschin, N., & Della Sala, S. (2004). Verbal recall in amnesiacs under conditions of diminished retroactive interference. *Brain, 127*, 825–834.
Cummings, J. L., Doody, R., & Clark, C. (2007). Disease-modifying therapies for Alzheimer disease: Challenges to early intervention. *Neurology, 69*, 1622–1634.
Davidson, J. E., Irizarry, M. C., Bray, B. C., Wetten, S., Galwey, N., Gibson, R., et al. (2010). An exploration of cognitive subgroups in Alzheimer's Disease. *Journal of the International Neuropsychological Society, 16*, 233–243.
De Mauro T. (2000). Il dizionario della lingua italiana per il terzo millennio. Paravia.
Della Sala, S., Cowan, N., Beschin, N., & Perini, M. (2005). Just lying there, remembering: Improving recall of prose in amnesic patients with mild cognitive impairment by minimising interference. *Memory, 13*, 435–440.
Dewar, M., Della Sala, S., Beschin, N., & Cowan, N. (2010). Profound retroactive interference in anterograde amnesia: What interferes? *Neuropsychology, 24*, 357–367.
Dewar, M., Fernández García, Y., Cowan, N., & Della Sala, S. (2009). Delaying interference enhances memory consolidation in amnesic patients. *Neuropsychology, 23*, 627–634.
Dudai, Y. (2004). The Neurobiology of consolidations, or, how stable is the engram? *Annual Review of Psychology, 55*, 51–86.
Fernández, G., & Tendolkar, I. (2006). The rhinal cortex: "Gatekeeper" of the declarative memory system. *Trends in Cognitive Sciences, 10*, 358–362.
Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). Mini-Mental State. A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research, 12*, 189–198.
Frisoni, G. B., Fox, N. C., Jack, C. R., Scheltens, P., & Thompson, P. M. (2010). The clinical use of structural MRI in Alzheimer disease. *Nature Reviews Neurology, 6*, 67–77.
Giovagnoli, A. R., Del Pesce, M., Mascheroni, S., Simoncelli, M., Laiacona, M., & Capitani, E. (1996). Trail making test: Normative values from 287 normal adult controls. *Italian Journal of Neurological Sciences, 17*, 305–309.
Hachinski, V. C., Iliff, L. D., Zilhka, E., Du Boulay, G. H., McAllister, V. L., Marshall, J., et al. (1975). Cerebral blood flow in dementia. *Archives of Neurology, 32*, 632–637.
Hughes, C. P., Berg, L., Danziger, W. L., Coben, L. A., & Martin, R. L. (1982). A new clinical scale for the staging of dementia. *The British Journal of Psychiatry, 140*, 566–572.
Iijima, T., Witter, M. P., Ichikawa, M., Tominaga, T., Kajiwara, R., & Matsumoto, G. (1996). Entorhinal–hippocampal interactions revealed by real-time imaging. *Science, 272*, 1176–1179.
Katz, S., Ford, A. B., Moskowitz, R. W., Jackson, B. A., & Jaffe, M. W. (1963). Studies of illness in the aged. The index of ADL: A standardized measure of biological and psychological function. *Journal of the American Medical Association, 185*, 914–919.
Locascio, J. J., Growdon, J. H., & Corkin, S. (1995). Cognitive Test Performance in detecting, staging, and tracking Alzheimer's Disease. *Archives of Neurology, 52*, 1087–1099.
Markesbery, W. R. (2010). Neuropathologic alterations in mild cognitive impairment: A review. *Journal of Alzheimer's Disease, 19*, 221–228.
McGeoch, J., & Nolen, M. (1933). Studies in retroactive inhibition IV. Temporal point of interpolation and degree of retroactive inhibition. *The Journal of Comparative Psychology, 15*, 407–417.
McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., & Stadlan, E. M. (1984). Clinical diagnosis of Alzheimer's Disease: Report of the NINCDS–ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology, 34*, 939–944.
Mensink, G. J., & Raaijmakers, J. G. (1988). A model for interference and forgetting. *Psychological Review, 95*, 434–455.
Morris, J. C. (2006). Mild cognitive impairment is early-stage Alzheimer Disease: Time to revise diagnostic criteria. *Archives of Neurology, 63*, 15–16.
Morris, J. C., Storandt, M., Miller, J. P., McKeel, D. W., Price, J. L., Rubin, E. H., et al. (2001). Mild cognitive impairment represents early-stage Alzheimer Disease. *Archives of Neurology, 58*, 397–405.
Orsini, A., Grossi, D., Capitani, E., Laiacona, M., Papagno, C., & Vallar, G. (1987). Verbal and spatial immediate memory span: Normative data from 1355 adults and 1112 children. *The Italian Journal of Neurological Sciences, 8*, 537–548.
Peigneux, P., Orban, P., Balteau, E., Degueldre, C., Luxen, A., Laureys, S., et al. (2006). Offline persistence of memory-related cerebral activity during active wakefulness. *PLoS Biology, 4*, 647–658.
Petersen, R. C. (2004). Mild cognitive impairment as a diagnostic entity. *Journal of Internal Medicine, 256*, 183–194.
Petersen, R. C., Roberts, R. O., Knopman, D. S., Boeve, B. F., Geda, Y. E., Ivnik, R. J., et al. (2009). Mild cognitive impairment: Ten years later. *Archives of Neurology, 66*, 1447–1455.
Petersen, R. C., Smith, G. E., Waring, S. C., Ivnik, R. J., Tangalos, E. G., & Kokmen, E. (1999). Mild cognitive impairment: Clinical characterization and outcome. *Archives of Neurology, 56*, 303–308.
Reisberg, B., Ferris, S., de Leon, M. J., & Crook, T. (1982). The Global Deterioration Scale for assessment of primary degenerative dementia. *American Journal of Psychiatry, 139*, 1136–1139.
Rössler, M., Zarski, R., Bohl, J., & Ohm, T. G. (2002). Stage-dependent and sector-specific neuronal loss in hippocampus during Alzheimer's Disease. *Acta Neuropathologica, 103*, 363–369.
Snodgrass, J. G., & Vanderwart, M. (1980). A standardized set of 260 pictures: Norms for name agreement, image agreement, familiarity, and visual complexity. *Journal of Experimental Psychology: Human Learning and Memory, 6*, 174–215.
Snowden, J., Stopford, C., Julien, C., Thompson, J., Davidson, Y., Gibbons, L., et al. (2007). Cognitive phenotypes in Alzheimer's Disease and genetic risk. *Cortex, 43*, 835–845.
Spinnler, H., & Tognoni, G. (Eds.). (1987). Standardizzazione e taratura italiana di test neuropsicologici. *Italian Journal of Neurological Sciences, 6*(Suppl. 8), 1–120.
Spinnler, H., & Della Sala, S. (1988). The role of clinical neuropsychology in the neurological diagnosis of Alzheimer's Disease. *Journal of Neurology, 235*, 258–271.
Stopford, C., Snowden, J., Thompson, J., & Neary, D. (2007). Distinct memory profiles in Alzheimer's Disease. *Cortex, 43*, 846–857.
Stopford, C. L., Snowden, J. S., Thompson, J. C., & Neary, D. (2008). Variability in cognitive presentation of Alzheimer's Disease. *Cortex, 44*, 185–195.
Welsh, K., Butters, N., Hughes, J., Mohs, R., & Heyman, A. (1991). Detection of abnormal memory decline in mild cases of Alzheimer's Disease using CERAD neuropsychological measures. *Archives of Neurology, 48*, 278–281.
Welsh, K. A., Butters, N., Hughes, J. P., Mohs, R. C., & Heyman, A. (1992). Detection and staging of Dementia in Alzheimer's Disease: Use of the neuropsychological measures developed for the consortium to establish a registry for Alzheimer's Disease. *Archives of Neurology, 49*, 448–452.
Winblad, B., Palmer, K., Kivipelto, M., Jelic, V., Fratiglioni, L., Wahlund, L.-O., et al. (2004). Mild cognitive impairment-beyond controversies, towards a consensus: Report of the International working group on Mild Cognitive Impairment. *Journal of Internal Medicine, 256*, 240–246.
Wixted, J. T. (2004). The psychology and neuroscience of forgetting. *Annual Review of Psychology, 55*, 235–269.
Yesavage, J. A., Brink, T. L., Rose, T. L., Lum, O., Huang, V., Adey, M., et al. (1983). Development and validation of a geriatric depression screening scale: A preliminary report. *Journal of Psychiatric Research, 17*, 37–49.
Zweig, H., & Campbell, G. (1993). Receiver-operating clinical (ROC) plots: A fundamental evaluation tool in clinical medicine. *Clinical Chemistry, 39*, 561–577.