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Neuronal correlates of serial position performance in amnestic mild cognitive impairment.

Title:

Neuronal correlates of serial position performance in amnestic MCI

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Abstract

Objectives:

Delayed recall of the first words of a list - the primacy position – is thought to be particularly dependent on intact memory consolidation. Hippocampal volume has been suggested as the primary neuronal correlate of delayed primacy recall in cognitively normal elderly individuals. Here, we studied the association of hippocampal volume with primacy recall in individuals with amnestic mild cognitive impairment (aMCI).

Methods:

We investigated serial position performance in 88 subjects with aMCI using a 16-word list (CVLT). Primacy and recency performance were measured during learning and delayed recall. Hippocampal volumes were automatically determined from structural MRI scans. We conducted regression analyses with bilateral hippocampal volumes as predictors and serial position indices as outcomes.

Results:

After controlling for age, gender, and total intracranial volume, bilateral hippocampal volume was not associated with primacy recall either during learning or delayed recall. Primacy performance during learning was associated with the right inferior and middle temporal gyrus as well as the right inferior parietal cortex and supramerginal gyrus. During delayed recall, primacy performance was related to the bilateral supramarginal gyri.

Conclusions:

Our findings suggest a reduced primacy effect in aMCI already during learning, contrasting previous findings in normal cognitive aging. This might indicate impaired encoding and consolidation processes at an early stage of episodic memory acquisition. Furthermore, our data indicates that hippocampal volume may not be a relevant determinant of residual primacy performance in the stage of aMCI, which may rather depend on temporal and parietal neocortical networks.

Keywords: amnestic MCI, Primacy, serial position effects, hippocampus, memory, Alzheimer's disease

1. Introduction

Impaired episodic memory, the main clinical feature of Alzheimer's disease (AD), reflects reduced encoding and consolidation (Carlesimo & Oscar-Berman, 1992). Encoding is the process of perceiving a stimulus and transforming it into a unit of information that can be stored in memory (Craik & Lockhart, 1972). Consolidation generally refers to the transfer of information from short-term memory into long-term memory, making it available for later retrieval, including after a delay (McGaugh, 2000). Successful recall performance, therefore, is considered an indicator of effective encoding and consolidation processes.

Serial position effects refer to the observation that words at the beginning of a list (primacy words) and words at the end of a list (recency words) are remembered typically better than words in the middle of a list ("primacy effect", or "recency effect", respectively) (Murdock Jr, 1962). While the recency effect is commonly thought to rely mainly on short-term memory (Atkinson & Shiffrin, 1971), the primacy effect is believed to emerge as a consequence of frequent rehearsal opportunities for early-list items, thus leading to the information being stored within long-term memory more effectively (Atkinson & Shiffrin, 1968). A preserved primacy effect may therefore be a particularly sensitive indicator for intact memory encoding and consolidation.

Encoding and consolidation processes strongly depend on hippocampal functioning (Wixted, 2004), although the exact role of the hippocampus in these processes is still a matter of debate. For example, it is not clear to date whether the hippocampus is involved in the consolidation process for only a limited amount of time, i.e., until the information has been transferred to association cortices (Squire, 1992); or whether the hippocampus is required to represent and re-encode the information each time it is remembered, so that memory contents are combined into a multiple-trace representation in the brain over the lifespan ("Multiple trace theory" (Nadel & Moscovitch, 1997)). Lesion and fMRI studies have investigated the association between hippocampal functioning and primacy as an indicator for consolidation

processes, e.g. (Hermann, et al., 1996; Strange, Otten, Josephs, Rugg, & Dolan, 2002). While these studies confirm a central role of the hippocampus, the extent of its contribution remains unclear compared to other brain structures such as frontal regions.

In normal cognitive aging, characteristic patterns of serial position effects are preserved even when overall recall performance is decreased (e.g. (Mitrushina, Satz, Chervinsky, & D'Elia, 1991)). Interestingly, in a group of 204 healthy older people, delayed recall performance of primacy words predicted subsequent global cognitive decline, as measured with the Mini Mental State Examination (MMSE), with higher accuracy than overall delayed recall performance (Bruno, Reiss, Petkova, Sidtis, & Pomara, 2013). This finding may indicate that primacy performance is a particularly sensitive indicator of incipient memory decline, possibly because of its high reliance on intact hippocampus function. Accordingly, among cognitively intact elderly individuals primacy performance was specifically associated with hippocampal volume as measured with structural MRI (Bruno, et al., 2015).

Serial position effects have also been found to discriminate between healthy cognitive aging, mild cognitive impairment (MCI) as a prodromal stage of dementia, and clinically manifest dementia in AD (Cunha, Guerreiro, de Mendonca, Oliveira, & Santana, 2012; Howieson, et al., 2011; Moser, et al., 2014). More specifically, the primacy effect was found to be reduced in MCI patients, and even more so in AD dementia patients, when compared to healthy elderly individuals (Cunha, et al., 2012; Howieson, et al., 2011; Moser, et al., 2014). In contrast, the recency effect in cohorts of MCI and especially in AD was found to be significantly increased, i.e., relatively more recency words were recalled compared to primacy and middle words. This could be due to relatively retained short-term memory as compared to long-term consolidation processes (Bäckman, Small, & Fratiglioni, 2001).

More recently, decreased primacy performance in delayed recall has been found to be a sensitive predictor of the conversion from MCI to AD (Egli, et al., 2014; Egli, et al., 2015). However, the neuronal correlates of primacy performance in patients with a manifest memory

impairment have not been investigated yet.

The present cross-sectional study aimed to examine neuronal correlates of primacy performance in a group of 88 individuals with amnestic MCI (aMCI). More specifically, we investigated whether and to what extent primacy performance in delayed recall is associated with MRI-measured hippocampal volume in amnestic MCI. Further, we compared this effect to the association of hippocampal volume with recency performance and total recall performance. In addition, unbiased whole brain analyses were used to explore which brain structures outside the hippocampus are associated with primacy performance in aMCI.

2. Methods

2.1. Participants

We included baseline data of 88 individuals with aMCI from a sample recruited for an intervention study conducted by the University Hospital Munich, Germany. The study received ethical approval by the local ethics committee of the Faculty of Medicine of the Ludwig-Maximilian University, Munich, Germany. All aMCI patients fulfilled the Peterson criteria (Petersen, et al., 1999): A) They described a subjective memory complaint, B) They showed memory performance of at least 1.5 SD below the age and education adjusted norm, assessed by the CERAD test battery, C) No clinically significant functional impairment of activities of daily living or manifest dementia were present, and D) CDR score was 0.5 in all cases)

All patients were characterized either as aMCI single domain (with a selective impairment of verbal memory or both verbal and figural memory, i.e., Z-score < -1.5) or aMCI multiple domain (with an impairment of memory as well as other cognitive domains, for example phonemic fluency) (Petersen, 2004; Petersen, et al., 2001). Our study sample consisted of 34 patients with aMCI single domain and 54 patients with aMCI multiple domain. The groups did not differ significantly in verbal episodic memory scores. Table 1 summarizes the

subjects' demographic and clinical characteristics including the statistical comparison between the MCI subgroups as well as the effect sizes. Figure 1 shows the CERAD performance.

2.2. Assessment of verbal episodic memory

Verbal episodic memory was assessed in detail using the "California Verbal Learning Test" (CVLT) (Delis, Kramer, Kaplan, & Ober, 1987). The CVLT is a standardized list-learning test and consists of two word lists (A and B) of 16 words each. The words belong to 4 semantic categories but are presented in a pseudo random order. First, list A is presented orally to the subject in five learning trials. After each trial, the subject is asked to freely recall the words. After that, a distractor list B is presented, and subjects are asked to recall the items from list B. Subsequently, subjects are requested to recall the items from list A ("immediate recall"). After a delay of 20 minutes, subjects perform a "delayed recall" (DR) test and a recognition trial.

We assessed the total recall scores by the proportion of correctly recalled words from all words (max. 16) for the learning phase and delayed recall. In accordance with previously published studies (Bruno, et al., 2013; Egli, et al., 2014), primacy performance was defined as the proportion of the number of correctly recalled items from the first four items of a word list. Recency performance was defined as the proportion of the number of correctly recalled items from the last four items. Finally, middle performance was defined as the proportion of correctly recalled items from the 8 middle positions between the primacy and recency words.

2.3 MRI

2.3.1 MRI-acquisition

MRI data were acquired with a single 3T Siemens Magnetom Verio Scanner (Siemens, Erlangen, Germany; software, syngo MR B17) in Munich, Germany, using a 12-channel head coil. T1-weighted, high-resolution structural MRI volumes of the brain were scanned using a

3-D magnetization-prepared rapid gradient-echo sequence (echo time (TE) = 3.06 ms, repetition time (TR) = 2100 ms, inversion time (TI) = 900 ms, bandwidth = 230 Hz per pixel, matrix = 240 x 256 x 160, isometric voxel size = 1.0 mm^3).

2.3.2 MRI processing

Processing of T1-MPRAGE images was conducted by using established methods of voxelwise morphometry (VBM) (Ashburner, 2009). T1-MPRAGE images were segmented into grey matter, white matter, and cerebrospinal fluid, and high-dimensionally registered to Montreal Neurological Institute (MNI) standard space, using a segmentation routine without reliance on tissue priors and the diffeomorphic DARTEL warping algorithm (Ashburner, 2007), implemented in the VBM8-toolbox in SPM 8. Warping parameters were applied to individual grey matter maps and voxel values were modulated to account for the volumetric differences introduced by the high-dimensional warps, such that the total amount of GM volume present before warping was preserved. The total intracranial volume (TIV) was calculated as the sum of the total segmented grey matter, white matter, and cerebrospinal fluid volumes in native space. For the voxel-wise whole brain analyses, warped grey matter maps were smoothed with a Gaussian smoothing kernel of 8mm full-width at half maximum.

For the Region of interest (ROI) analyses, individual grey matter volumes of the left and right hippocampus were automatically extracted from the warped grey matter segments by summing up the modulated voxel values using a predefined hippocampus mask in template space (before smoothing). This mask was obtained by manual delineation of the hippocampus in the MNI standard space template used for spatial normalization. Tracing of the hippocampus outlines followed recently developed international consensus criteria for manual hippocampus segmentation on MRI (Boccardi, et al., 2013); http://www.hippocampal-protocol.net/SOPs/index.php) and was performed by a certified tracer (MJG) using MultiTracer 1.0 software (http://www.loni.usc.edu/Software/MultiTracer).

This approach extends previously validated automated volumetry approaches within SPM software by incorporating high-dimensional image normalization (Firbank, Barber, Burton, & O'Brien, 2008), which has been shown to further increase the performance of such automated volumetry approaches (Klein, et al., 2009).

2.4. Statistical analysis

Behavioral data

Serial position effects were compared both WITHIN and ACROSS the recall phases (learning phase and delayed recall). Due to non-normally distributed test variables, Wilcoxon Tests for between group comparisons were used. The significance level was set to $p < 0.05$.

As many subjects scored zero in the recall phase, we tested for a possible floor effect by performing a secondary analysis after the exclusion of subjects with a score of zero in DR. Thus 66 individuals were included in this analysis.

MRI data

For the ROI-based analysis, we performed separate multiple linear regression analyses of left and right hippocampal grey matter volume on total recall, primacy, and recency performance for the learning phase and DR separately. The control variables were age, gender, education, total intracranial volume (TIV) and the aMCI subtype. Due to normally distributed residuals, we decided to use regression models despite of partial variable skewness.

For the complementary whole brain analyses, total recall, primacy, and recency performance were used as predictor variables in separate voxel-wise regression models controlling for the covariates age, gender, education, TIV, and the aMCI subtype. With a minimal cluster size of 50 voxels, the statistical threshold was set to $p < 0.001$, uncorrected for multiple comparisons.

To account for floor effects, we reanalyzed the MRI data in the same way as the behavioral data (excluding individuals who scored zero in DR, 66 individuals were included in the re-analysis).

3. Results

3.1. Behavioral Data

The CVLT total recall and serial position performances are presented in Figure 2. WITHIN the learning phase (CVLT-Trials 1-5), recency performance was significamtly higher thanprimacy performance (Z (N=88) = -6.675, p < .001) as well as significantly higher than middle performance (Z (N=88) = -7.881, p < .001). Primacy performance was significantly higher than middle performance (Z (N=88) = -3.815, p < .001).

For delayed recall (DR), primacy performance revealed the highest value, and was significantly different from recency performance (Z (N=88) = -3.926, p < .001), but not from middle performance (Z (N=88) = -1.666, p = .096). Recency performance was significantly lower than middle performance (Z (N=88) = -2.672, p = .008).

Comparing serial position effects ACROSS the different recall phases, recency performance was significantly lower in DR compared to the learning phase (Z (N=88) = -7.719, p < .001). There were no differences between the learning phase and DR for both primacy performance (Z (N=88) = -1.218, p = .223) and middle performance (Z (N=88) = -.066, p = 0.947).

3.2. MRI Data

3.2.1 ROI analyses

Serial position performance:

We found no significant associations between hippocampal volumes and primacy or recency performance, respectively, neither in the learning phase nor in DR. Excluding subjects with a score of zero in DR did not change the results.

Total Recall performance:

Both left and right hippocampal volumes were significant predictors of total recall performance in the **learning phase**. The regression model including the main predictor of left

hippocampal volume ($p = 0.002$, $\beta = 0.322$, partial $R = 0.332$) and all control variables explained around 40 percent of the variance ($R^2 = 0.404$, $F = 10.82$, $p < 0.0001$).

The model including the main predictor of right hippocampal volume ($p = 0.012$, $\beta = 0.259$, partial $R = 0.274$) explained 38 percent of the variance ($R^2 = 0.380$, $F = 9.90$ $p < 0.0001$).

In the regression models of **DR** ($R^2 = 0.393$ $F = 10.40$, $p < 0.0001$), only the left hippocampal volume, but not right volume was a significant predictor ($\beta = 0.268$, $p = 0.011$, partial $R = 0.278$).

3.2.2 Whole Brain analyses

Table 2 reports the peak-level coordinates and cluster sizes of the whole-brain voxel-based regression analyses.

Primacy performance:

Primacy in the learning phase showed significant associations with grey matter volume in the left inferior parietal lobe, the left supramarginal gyrus and right middle and inferior temporal gyrus (Figure 3a). DR primacy performance was only significantly associated with grey matter volume in the bilateral supramarginal gyrus (Figure 3a).

Recency performance:

Recency in the learning phase showed significant associations with grey matter volume in the left middle and inferior temporal gyrus, as well as the left occipital and frontal pole (Figure 3b). DR recency performance was associated with right supramarginal gyrus, right frontal orbital cortex, amygdala bilaterally, and cerebellar cortex (Figure 3b).

Total recall performance:

Total recall performance in the learning phase showed significant associations with bilateral clusters of grey matter volume in the superior and middle temporal gyrus, cerebellar cortex, amygdala, as well as in the left hippocampus and parahippocampal gyrus (see figure 3c). In addition, smaller clusters were found in the left supramarginal gyrus and right cingulate cortex as well as the orbital-frontal cortex. Total DR performance was associated with volume

of the bilateral supramarginal gyrus, the left angular gyrus and the left amygdala (Figure 3c). Overall, the results did not change after the exclusion of subjects with a score of zero in DR.

4. Discussion

Our study investigated associations between serial position effects, particularly primacy performance in a verbal memory task and hippocampus gray matter volume in a group of aMCI subjects. The behavioral data showed a primacy effect during the learning phase that was much lower than the recency effect. During delayed recall (DR), no primacy effect was observed. In addition, hippocampal volume was not significantly associated with the primacy performance, neither during learning nor DR. A whole brain analysis revealed parieto-temporal structures to be involved in the remaining primacy performance in aMCI.

We found that primacy recall during the learning phase was significantly better than recall of words in the middle of the list. However, the primacy effect was significantly lower than the recency effect. This is in contrast to the performance of healthy individuals who show no difference between primacy and recency effects during learning on similar tasks (Mitrushina, et al., 1991), but confirms previous findings in individuals with MCI (Cunha, et al., 2012; Howieson, et al., 2011; Martín, et al., 2013).

However, the difference between primacy and recency effects during the learning phase seemed to be higher in the present study than in previous studies (for example (Cunha, et al., 2012)). The performance of our aMCI subjects appeared similar to patients with manifest AD who typically present a notable recency effect (Cunha, et al., 2012; Foldi, Brickman, Schaefer, & Knutelska, 2003; Howieson, et al., 2011; Martín, et al., 2013). The difference between our and previous MCI studies may be related to the different selection criteria of the samples. We investigated only aMCI subjects, while in other studies both amnestic and non-amnestic MCI subjects were included, or the primary domain of cognitive impairment was not further specified (Egli, et al., 2014). This may lead to pronounced differences in serial

position effects. For example, Moser et al. (2014) (Moser, et al., 2014) showed that patients with amnestic MCI, but not individuals with non-amnestic MCI exhibited a pattern of relatively small primacy effect compared to a notable recency effect, whereas individuals with non-amnestic MCI presented with a profile similar to that of older healthy persons with no difference between primacy and recency effect. A reduced primacy compared to a much more pronounced recency effect during learning implies that encoding and rehearsal processes are already affected at an early stage of information acquisition in amnestic MCI.

With regard to DR, our study data showed no primacy effect. This finding is in contrast to Martin et al. 2013 (Martín, et al., 2013), the only previous publication that also investigated serial position effects in delayed recall in MCI patients (Martín, et al., 2013). However, compared to Martin et al's sample, our data showed a less pronounced primacy effect during the learning phase, possibly reflecting a disturbed early consolidation process followed by a less successful transfer of information into long-term storage. The strongly reduced recency effect during delayed recall in our sample appears consistent with the findings of Martin et al. (Martín, et al., 2013).

Future longitudinal studies will have to investigate the use of serial position effects compared to established memory indexes for the prediction of cognitive decline and conversion to dementia. While there are numerous studies suggesting serial position effects to be more sensitive than global recall in measuring episodic memory and predicting cognitive decline (Bruno, Reiss, Petkova, Sidtis, & Pomara, 2013; Egli, et al., 2014; Egli, et al., 2015), other studies comparing the sensitivity and specificity of memory indices did not find evidence for a high discriminability between different indices (Boone, Lu, & Wen, 2005).

In contrast to findings reported for cognitively intact older people (Bruno, et al., 2015), primacy performance in our MCI sample was not associated with hippocampal volume during learning or DR. This finding was replicated both in the ROI and the voxel based whole brain analysis. Hippocampal atrophy is usually considered an early sign of AD (Jack, et al., 2000),

possibly resulting in decreased consolidation which is reflected by a disappearing primacy effect (as obvious in our behavioral data). The reduced primacy effect and the lack of association of primacy performance with hippocampal volume may suggest that the contribution of the hippocampus to memory consolidation declines in the disease progression of AD and other neuronal networks become more relevant for consolidation and potentially compensate for the loss of hippocampus function with disease progression.

Consistent with this argumentation, in the whole brain voxel-based analysis, we found inferior parietal structures such as the supramarginal gyrus and the inferior parietal cortex, associated with the primacy performance during both learning and delayed recall. In general, these areas are involved in encoding of information and reflect the phonological buffer in short time memory (Paulesu, Frith, & Frackowiak, 1993). An fMRI study by Sommer et al. 2006 (Sommer, Rose, & Buchel, 2006) investigated neuronal correlates of the primacy effect in healthy individuals: for the primacy performance, an involvement of the inferior-parietal gyrus and angular gyrus was found. The authors argued that due to their initial position, primacy words need a particularly efficient encoding. As we found inferior-parietal rather than hippocampal involvement, we would assume that encoding is preserved in MCI, and the primacy effect involves a higher proportion of short term memory processes in MCI-patients than in healthy older people.

Further structures associated with the primacy performance during learning were the right middle and inferior temporal gyrus (32). These areas are involved in perceiving (Cabeza & Nyberg, 2000) and recognizing objects (Chao, Haxby, & Martin, 1999). As perceiving a stimulus is a first step in the process of encoding, these findings confirm the importance of the encoding phase for learning in MCI patients.

Our whole brain analysis showed only a weak relationship between total recall and hippocampal gray matter volume in the learning phase. In contrast, we observed a strong association with the amygdala. One may assume that consolidation function driven by the

medial limbic circuit (Shah, Jhawar, & Goel, 2012) in normal individuals is increasingly taken over by basolateral limbic structures in the course of disease progression of AD (Sarter & Markowitsch, 1985). However, one single fMRI study showed rather frontal compensatory activity within the medial limbic circuit (Browndyke, et al., 2013). Further research is needed to resolve this question.

As expected, with regard to the recency performance, no associations with the hippocampus were observed. This is in line with the suggested reliance of recency performance on short term memory processes independent of hippocampal function (Davelaar, Goshen-Gottstein, Ashkenazi, Haarmann, & Usher, 2005).

One major limitation of our study is the small variance with regard to serial position performance and considerable floor effects. We attempted to minimize this confound by excluding zero results in the behavioral data. A further limitation are the sample characteristics. Although diagnosis of MCI used well established criteria (Petersen, et al., 1999), biomarker supported diagnosis could not be provided in all cases.

Another methodological aspect that has to be discussed is the liberal statistical threshold in the voxel based analyses. Our ROI approach was hypothesis driven; we expected to find an association between hippocampal volume and primacy performance in our MCI cohort. However, effects were not significant. Since we did not use multiple comparison correction, the probability of a type 2 error (i.e., rejecting an effect although it is present) was low. The low type 2 error probability suggests a robust lack of association between primacy performance and hippocampus volume. Additionally, we were interested in identifying potential alternative neuronal networks. For this purpose, we used an exploratory whole brain analysis. Again with a low probability for type 2 errors, these voxel based findings confirmed the absence of an effect in the hippocampus.

In summary, our findings suggest that individuals with aMCI already show a reduced primacy effect during the learning phase of episodic memory tests. This is different to previous

findings in normal cognitive aging and probably indicates impaired encoding and consolidation processes at an early stage of episodic memory acquisition. As a consequence, hippocampal volume seems to be a less relevant determinant of the residual primacy effect in aMCI; the remaining primacy performance in MCI depends rather on the integrity of temporal and parietal neocortical networks.

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Competing Interests

The authors have declared that no competing interests exist.

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Legends of tables and figures

Table 1 Demographical and clinical data

SD = standard deviation; CERAD = Consortium to Establish a Registry for Alzheimer's Disease;MMSE = Mini Mental State Examination
*The subjects' education levels were converted to a categorical scale based on the German education system, ranging from 1 (i.e., no educational qualification) to 5 (i.e., university degree).

Table 2 *Results from Whole brain linear regression models including all control variables*

DR = Delayed recall, L = left, R = right

Figure 1: Cognitive performance of CERAD subtests

Figure 2 *CVLT total recall and serial position performances within each recall phase*

Figure 3a *Whole brain regression analyses – primacy performance as predictor*

Voxel-based analyses of the associations between primacy performance and regional gray matter volumes in the learning phase and delayed recall. Effects of primacy performance on regional gray matter volume are shown on coronal sections through the MNI space template. With a minimal cluster size of 50 voxels, the statistical threshold was set to $p < 0.001$, uncorrected for multiple comparisons.

Figure 3b *Whole brain regression analyses –Recency performance as predictor*

Voxel-based analyses of the associations between recency performance and regional gray matter volumes in the learning phase and delayed recall. Effects of recency performance on regional gray matter volume are shown on coronal sections through the MNI space template. With a minimal cluster size of 50 voxels, the statistical threshold was set to $p < 0.001$, uncorrected for multiple comparisons.

Figure 3c *Whole brain regression analyses – total recall performance as predictor*

Voxel-based analyses of the associations between recall performance and regional gray matter volumes in the learning phase and delayed recall. Effects of total recall performance on regional gray matter volume are shown on coronal sections through the MNI space template.

With a minimal cluster size of 50 voxels, the statistical threshold was set to $p < 0.001$, uncorrected for multiple comparisons.

Figure1

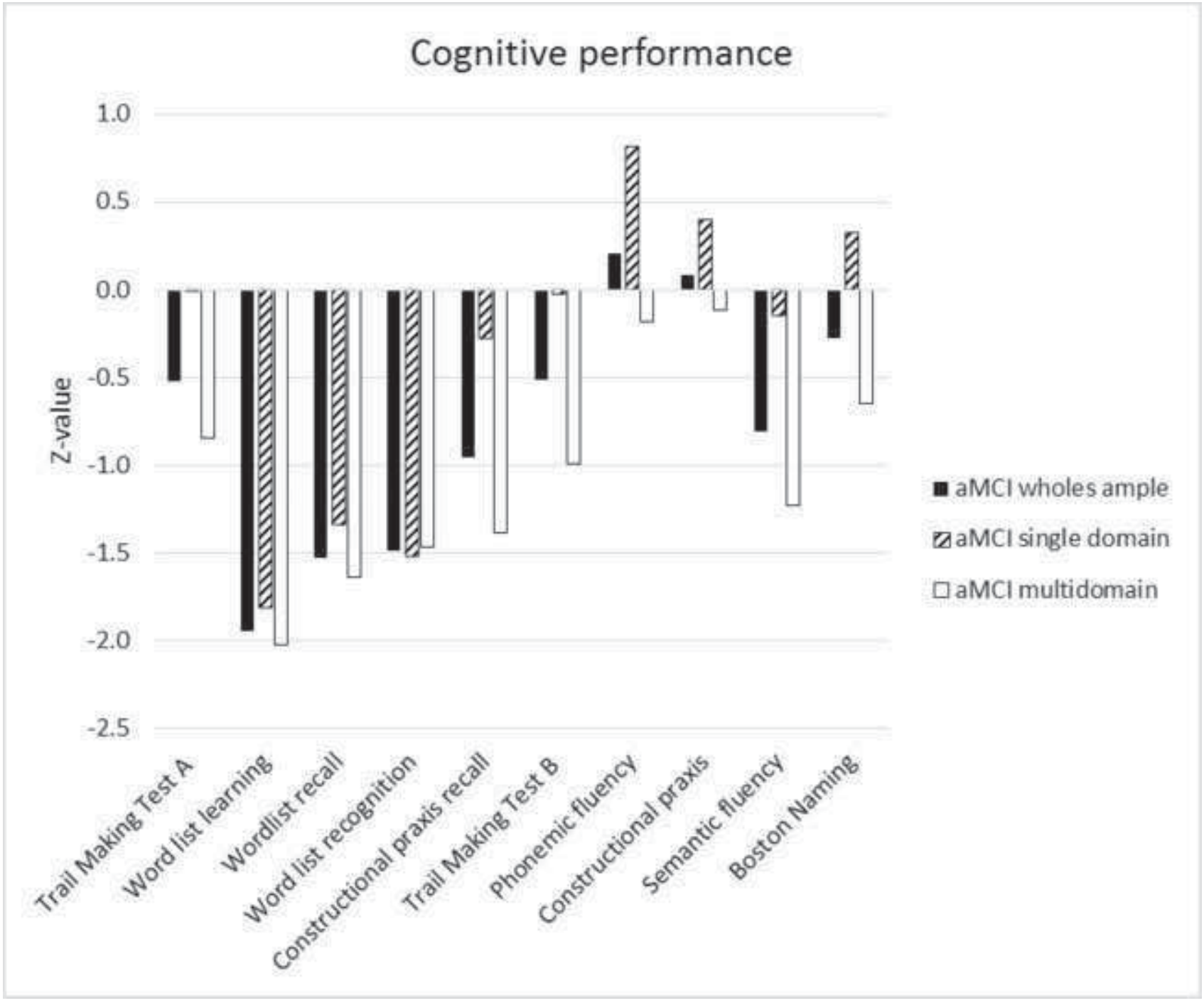
Cognitive performance
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
Z-value
Trail Making Test A
Word list learning
Wordlist recall
Word list recognition
Constructional praxis recall
Trail Making Test B
Phonemic fluency
Constructional praxis
Semantic fluency
Boston Naming
aMCI wholes ample
aMCI single domain
aMCI multidomain

Figure2

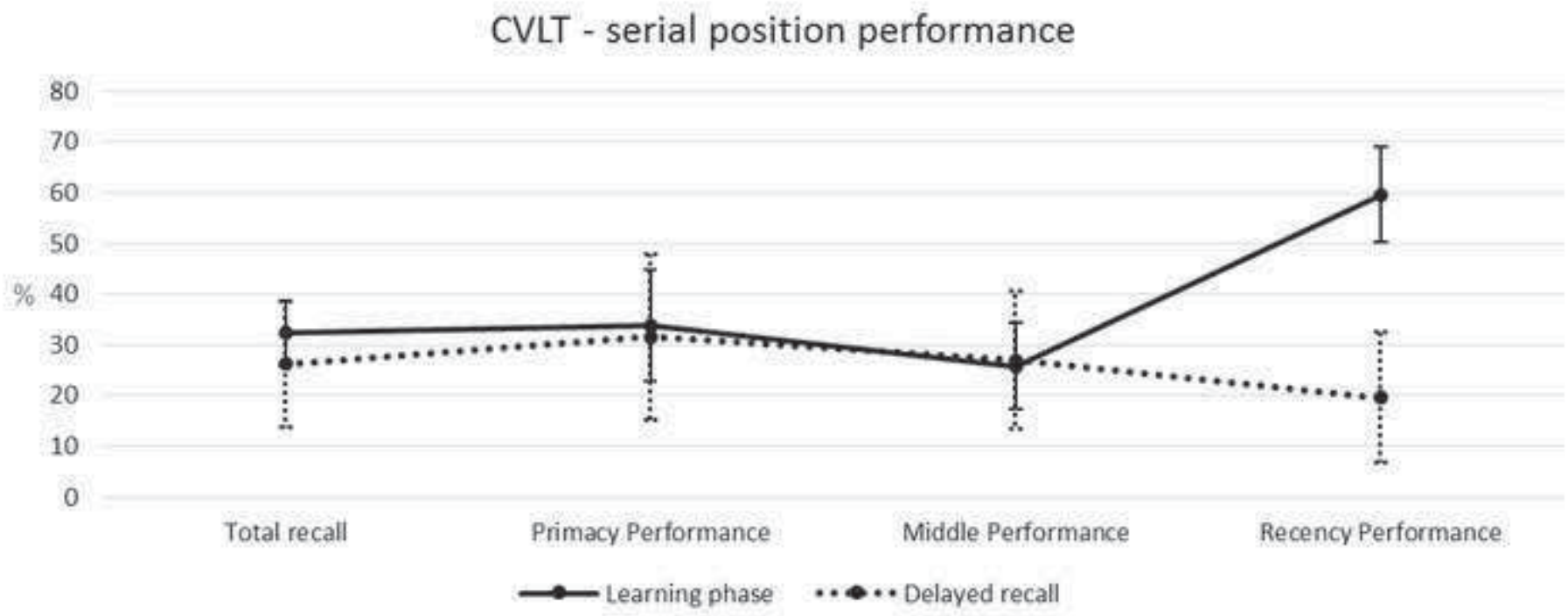
CVLT - serial position performance
80
70
60
50
% 40
30
20
10
0
Total recall
Primacy Performance
Middle Performance
Recency Performance
Learning phase
Delayed recall

Figure3a

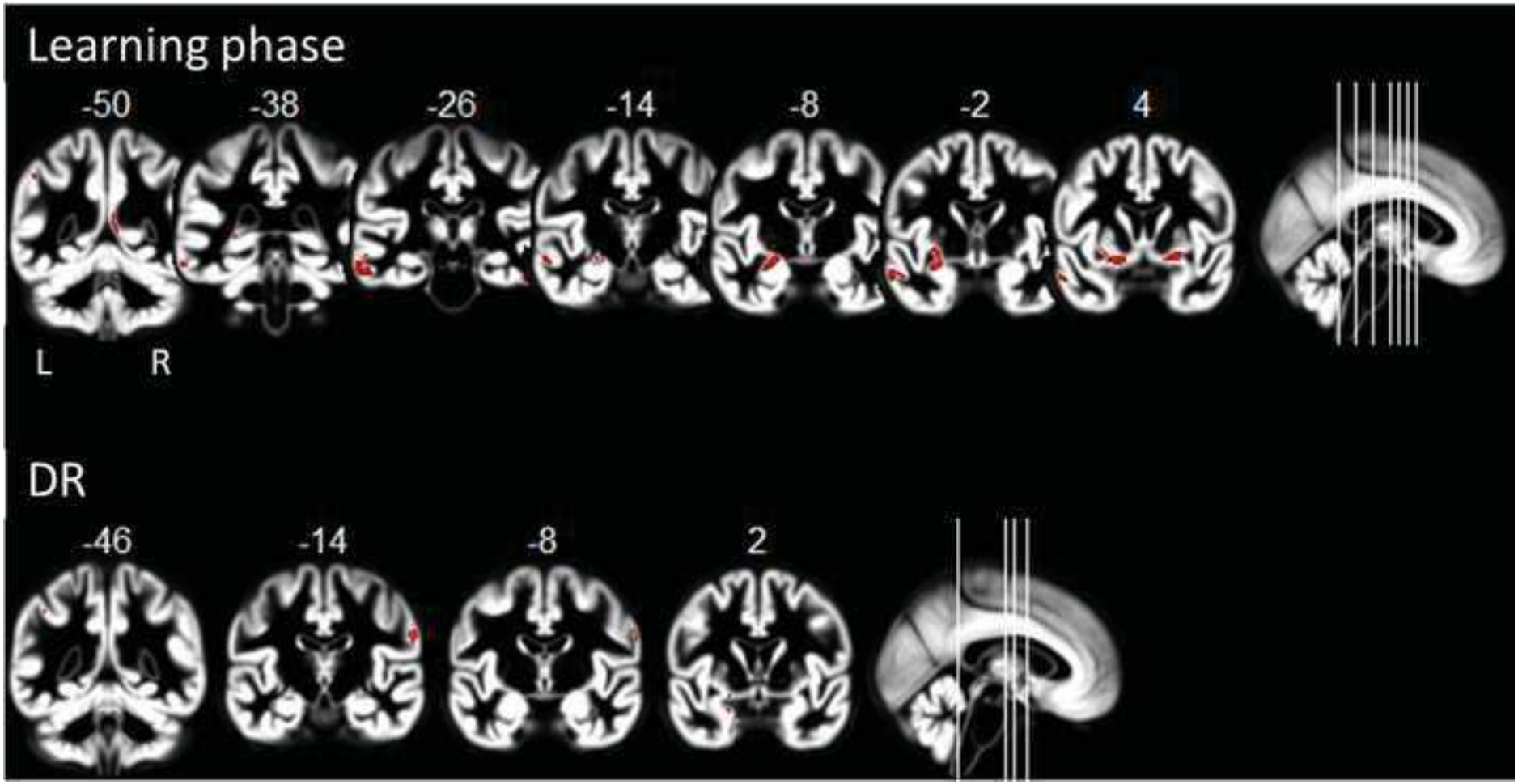

Figure3b

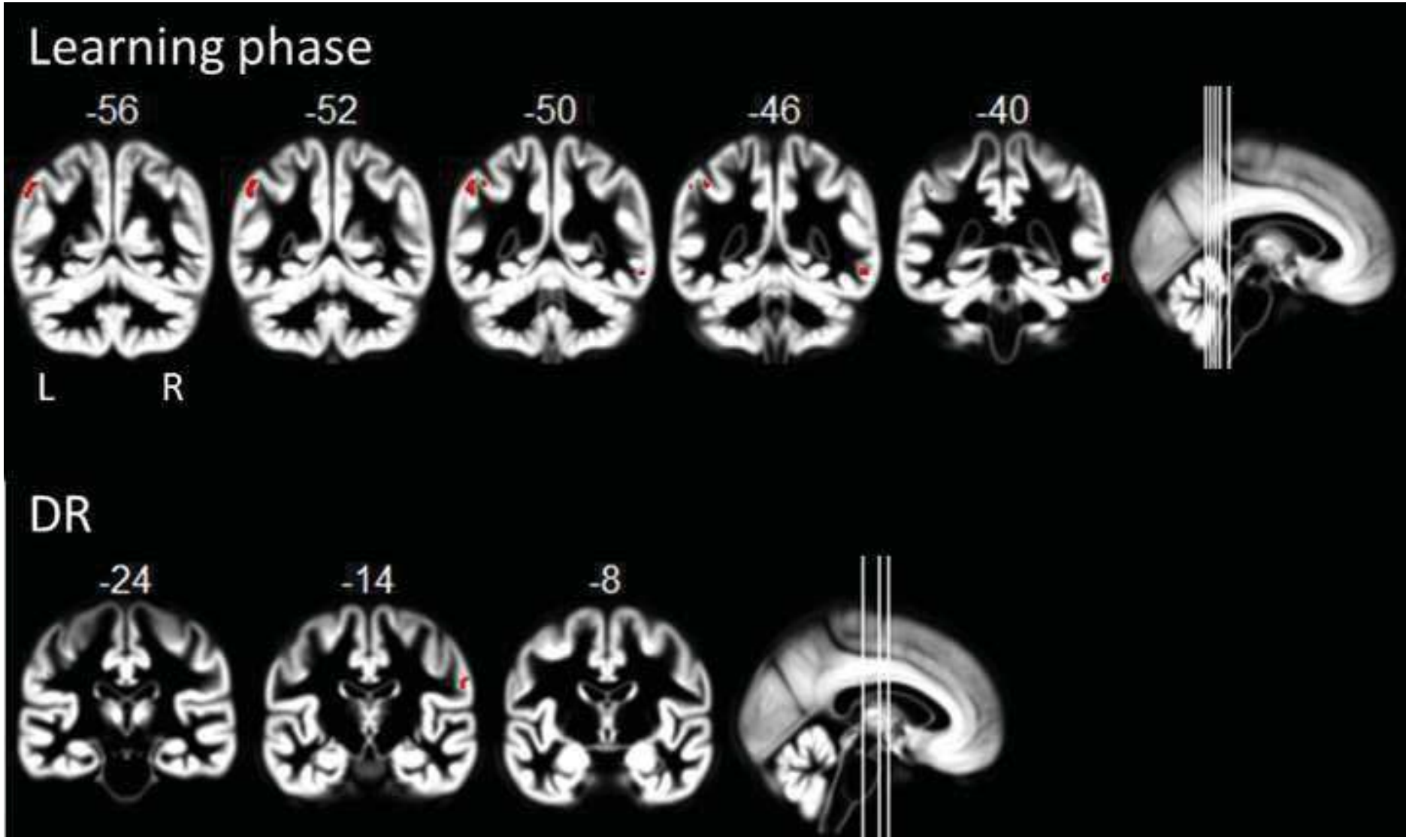

Figure3c

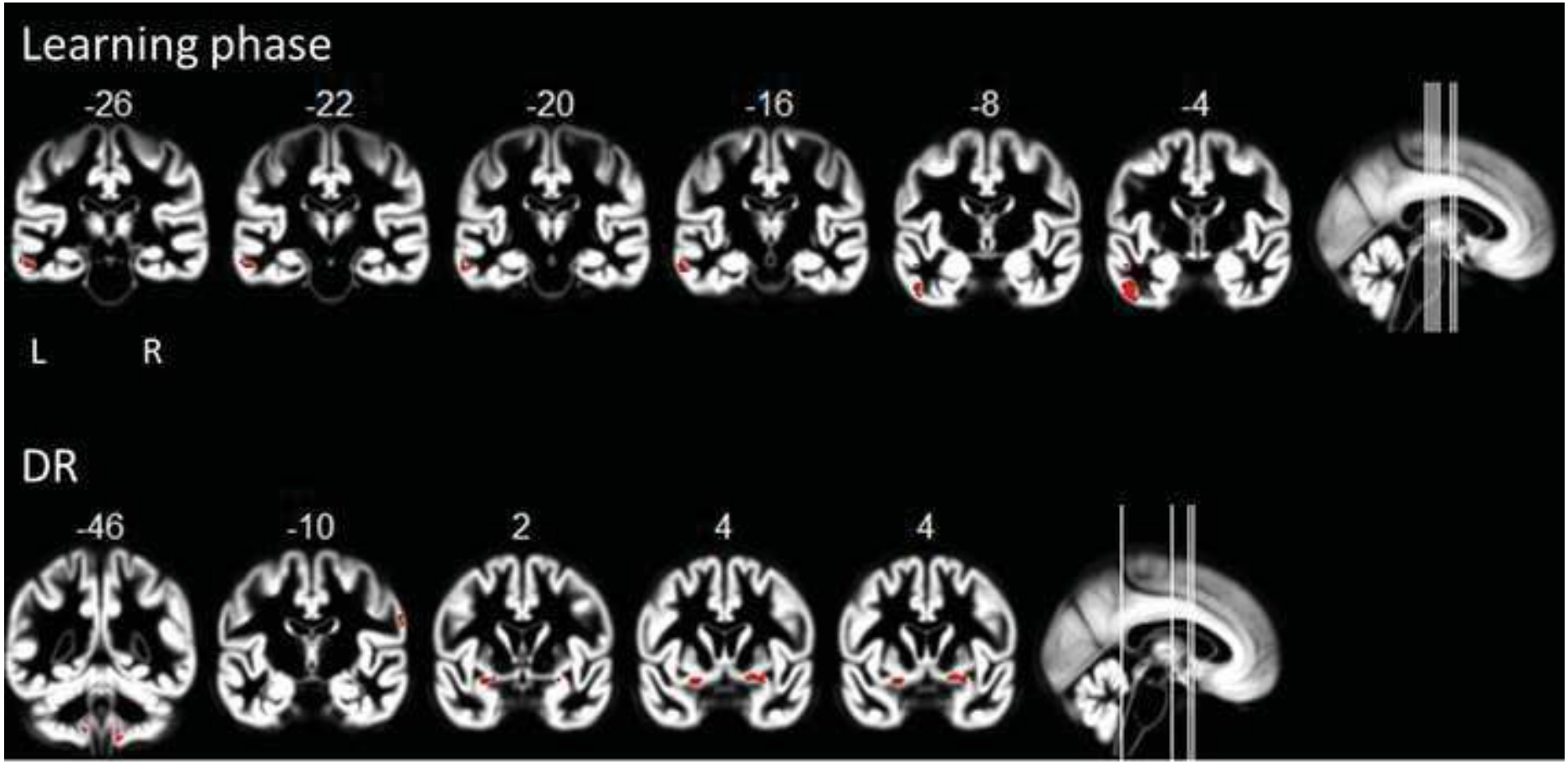

Table 1 Demographical and clinical data

	Total sample (N=88)				**aMCI single domain (N=34)**				**aMCI multi domain (N=54)**				**aMCI single domain vs. aMCI multi domain**
	Mean	**SD**	**Range**		**Mean**	**SD**	**Range**		**Mean**	**SD**	**Range**		**effect size [a]**
Demographics													
Age (years)	74.1	5.58	61.0	87.0	73.3	5.98	61.0	85.0	74.6	5.31	65.0	87.0	0.23
Gender (N male/female)	44/44				12/22				32/22				0.23
Education [b] (1/2/3/4/5)	0/24/23/19/22				0/14/6/7/7				0/10/17/12/15				0.26
Cognitive Performance (CERAD)													
MMSE	27.3	1.69	22.0	30.0	27.9	1.58	24.0	30.0	26.8	1.63	22.0	30.0	-0.68**
Word list learning	-1.9	0.96	-4.2	0.6	-1.8	0.89	-4.0	0.6	-2.0	1.01	-4.2	0.2	-0.21
Word list recall	-1.5	0.92	-4.2	0.3	-1.4	0.81	-2.9	0.3	-1.6	0.97	-4.2	0.0	-0.22
Word list recognition	-1.5	1.37	-5.3	0.9	-1.5	1.64	-5.3	0.9	-1.5	1.18	-5.0	0.7	0.00
Constructional praxis recall	-1.0	1.46	-3.4	2.5	-0.3	1.59	-3.0	2.5	-1.4	1.21	-3.4	1.3	-0.80***
Trail Making Test A	-0.5	1.03	-3.2	1.9	0.0	0.96	-1.8	1.9	-0.8	0.95	-3.2	1.7	-0.84***
Trail Making Test B	-0.5	1.13	-2.5	2.9	0.0	0.99	-2.4	1.5	-1.0	1.06	-2.5	2.9	-0.97***
Phonemic fluency	0.2	1.22	-3.4	2.8	0.8	1.17	-2.6	2.8	-0.2	1.09	-3.4	2.0	-0.89***
Constructional praxis	0.1	1.19	-2.5	1.7	0.4	1.13	-2.4	1.7	-0.1	1.20	-2.5	1.6	-0.43*
Semantic fluency	-0.8	1.10	-3.7	2.5	-0.1	0.87	-1.4	2.5	-1.2	1.02	-3.7	0.9	-1.14***
Boston Naming Test	-0.3	1.27	-3.6	1.6	0.3	0.93	-1.4	1.6	-0.7	1.32	-3.6	1.6	-0.84***

SD = standard deviation; CERAD = Consortium to Establish a Registry for Alzheimer's Disease; MMSE = Mini Mental State Examination; levels of significance: *p<0.05, **p<0.01, ***p<0.001

[a] Cohen's d (cohen's w for gender and education)

[b] The subjects' education levels were converted to a categorical scale based on the German education system, ranging from 1 (i.e., no educational qualification) to 5 (i.e., university degree).

Table 2 *Results from Whole brain linear regression models including all control variables*

Serial position performance			cortical area	cluster size	peak T values	MNI-coordinates		
						x	y	z
Primacy	**Learning**	L	inferior parietal lobe	603	4.18	-48	-49	43
		R	middle temporal gyrus	148	3.73	69	-39	-15
		R	inferior temporal gyrus	58	3.72	54	-48	-11
		L	supramarginal gyrus	77	3.65	-48	-22	30
	DR	L	supramarginal gyrus	76	3.75	-45	-24	31
		R	supramarginal gyrus	96	3.62	58	-12	22
Recency	**Learning**	R	occipital pole	60	4.51	20	-91	10
		L	inferior temporal gyrus	516	4.79	-51	-25	-18
		L	frontal pole	69	3.92	-36	41	10
		L	inferior temporal gyrus	447	4.20	-48	-3	-45
	DR	R	supramarginal gyrus	270	3.79	60	-12	27
		R	cerebellum	137	3.90	12	-46	-53
		L	cerebellum	106	3.56	-10	-48	-50
		R	amygdala	111	3.54	26	4	-17
		L	amygdala	118	3.55	-16	2	-15
Total Recall	**Learning**	L	middle temporal gyrus	1045	5.00	-56	-28	-14
		L	amygdala parahippocampal gyrus	1245	4.51	-30	-3	-15
		R	cingulate gyrus	517	4.38	10	-42	3
		L	hippocampus	196	4.11	-28	-34	4
		L	supramarginal gyrus	252	3.71	-46	-45	43
		R	cerebellum	58	3.75	15	-48	-50
		L	middle temporal gyrus	270	3.64	-46	-4	-27
		R	frontal orbital cortex	260	3.66	21	9	-11
		R	inferior temporal gyrus	118	3.85	51	-22	-23
	DR	L	supramarginal gyrus, angular gyrus	195	3.80	-54	-58	48
		L	amygdala	165	3.73	-15	0	-14
		R	supramarginal gyrus	473	3.78	69	-4	21

DR = Delayed recall, L = left, R = right