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Training-related brain plasticity in subjects at risk of developing Alzheimer's disease

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Subjects with mild cognitive impairment are at risk of developing Alzheimer's disease. Cognitive stimulation is an emerging intervention in the field of neurology and allied sciences, having already been shown to improve cognition in subjects with mild cognitive impairment. Yet no studies have attempted to unravel the brain mechanisms that support such improvement. This study uses functional magnetic resonance imaging to measure the effect of memory training on brain activation in older adults with mild cognitive impairment and to assess whether it can reverse the brain changes associated with mild cognitive impairment. Brain activation associated with verbal encoding and retrieval was recorded twice prior to training and once after training. In subjects with mild cognitive impairment, increased activation was found after training within a large network that included the frontal, temporal and parietal areas. Healthy controls showed mostly areas of decreased activation following training. Comparison with pre-training indicated that subjects with mild cognitive impairment used a combination of specialized areas; that is, areas activated prior to training and new alternative areas activated following training. However, only activation of the right inferior parietal lobule, a new area of activation, correlated with performance. Furthermore, the differences between the brain activation patterns of subjects with mild cognitive impairment and those of healthy controls were attenuated by training in a number of brain regions. These results indicate that memory training can result in significant neural changes that are measurable with brain imaging. They also show that the brains of people with mild cognitive impairment remain highly plastic.

Keywords: mild cognitive impairment; Alzheimer's disease; memory training; neuroimaging; functional MRI; brain plasticity

Abbreviations: MCI = mild cognitive impairment

Introduction

Older subjects with mild cognitive impairment (MCI) are at high risk of being in a prodromal phase of Alzheimer's disease (Petersen *et al.*, 1999, 2001; Gauthier *et al.*, 2006). Although they exhibit impaired episodic memory (Petersen *et al.*, 1999; Morris *et al.*,

2001; Hudon *et al.*, 2006; see Belleville *et al.*, 2008 for a review), such individuals fail to meet criteria for dementia. Still, this prodromal phase of Alzheimer's disease may be a key period for providing interventions meant to promote brain plasticity and reduce cognitive symptoms. Accumulating evidence suggests that training that relies on the teaching of visual or semantic

mnemonics can improve episodic memory in individuals in this phase (Belleville *et al*., 2006; Belleville, 2008; Rozzini *et al*., 2007). The goal of this study was to use functional MRI of the brain to provide critical information regarding the presence, extent and nature of the underlying brain plasticity in subjects with mild cognitive impairment who received memory intervention. In the light of recent neural models that suggest healthy ageing is accompanied by significant brain plasticity (Cabeza, 2002), it is crucial to determine whether the ageing brain retains its plasticity when entering the early phases of age-associated neurodegenerative diseases and how current models of brain plasticity apply to subjects at risk for neurodegenerative diseases.

Cognitive training has been suggested as a means by which older adults can improve their memory in a lasting manner (Willis *et al*., 2006). In addition, training can provide information on the extent and mechanisms of brain plasticity in older adults. Training data can contribute to our understanding of the nature and extent of brain plasticity in ageing and to models of brain plasticity in the ageing brain. The HAROLD (hemispheric asymmetry reduction in older adults) model proposes that brain compensation in healthy ageing relies on the recruitment of homologous regions in the hemisphere opposite to the one specialized for the impaired process, resulting in a reduced hemispheric asymmetry (Cabeza, 2002). The CRUNCH (compensation-related utilization of neural circuits hypothesis) model proposes that compensation following brain insult might result in a combination of increased recruitment of specialized brain areas normally involved in the recruitment process and the recruitment of new brain areas, depending on the degree of demand of the task (Reuter-Lorenz and Lustig, 2005). In contrast, mechanisms of dedifferentiation would reflect the inability of the impaired brain to recruit specialized brain areas efficiently (Li and Lindenberger, 1999; Logan *et al*., 2002), which would result in the increased activation of contralateral brain regions. These models make different predictions regarding the effect of memory training on brain activation. The HAROLD model predicts that training should increase bilateral recruitment. According to the CRUNCH model, areas that are normally specialized for memory might show increased activation following training, but training might also result in the recruitment of alternative networks. In turn, dedifferentiation predicts increased recruitment in specialized areas and reduced recruitment of contralateral regions following training. In both the HAROLD and CRUNCH models, increased activation should correlate with improvement; no such relation is expected in the dedifferentiation view. The pattern of changes in brain activation might also shed light on how the intervention works at the cognitive and neural levels. The presence of increased activation following training in areas that were not activated prior to training would indicate a reliance on new alternative strategies (Lustig *et al*., 2009). In contrast, decreased activation in previously recruited areas would suggest that the intervention led to a more efficient use of those areas or resulted from a reduced necessity for the compensatory use of an atypical region.

The few empirical results for older adults support a combination of increased specialized and alternative networks following memory training. Nyberg *et al*. (2003) found that healthy adults (younger and older), who successfully used a mnemonic based on visual imagery, showed increased activation in the left parieto-occipital cortex, a region involved in visual imagery. Although they did not actually use a memory-training paradigm, Logan *et al*. (2002) found that, when provided with semantic encoding cues, healthy older adults showed activation in left prefrontal regions that were initially under-recruited in comparison with younger adults. Both studies suggest that the brains of healthy older adults retain their ability to recruit new networks following training and hence retain their plasticity. However, nothing is known regarding the effect of memory training on the pattern of brain activation in subjects in an early phase of or at risk of developing Alzheimer's disease and whether similar effects would be observed with respect to current models of age-related plasticity.

In this study, we measured the training-related brain activation in older adults meeting criteria for MCI (Petersen, 2003). The intervention targeted episodic memory, as this is the major domain of complaint and deficit (Petersen *et al*., 2001). Previous work showed that the type of intervention used here improved delayed word recall and face-name memory in subjects with MCI and increased their self-reported memory functioning in daily life (Belleville *et al*., 2006). The training programme was designed to help individuals with MCI develop and maintain efficient episodic memory encoding and retrieval strategies by relying on remaining capacities and strengths. Here, we trained them to implement strategies that depend on their semantic knowledge and visual imaging capacities. Because the intervention relies on alternative encoding and retrieval strategies, it was expected to produce new activations in areas that are not typically associated with memory, but that are involved in visuospatial and/or semantic processing. Furthermore, it was found that subjects with MCI are not as efficient at initiating elaborate encoding and retrieval strategies (Hudon *et al*., in press; Froger *et al*., 2009). For this reason, the intervention was expected to result in increased activation in parts of the attentional network.

An innovative methodological aspect of our study is the use of participants as their own controls in order to control for repetition effects. Indeed, some studies have reported that repeating the functional MRI examination might result in decreased activation because of a reduction in arousal and stress associated with the novelty of the testing condition (Loubinoux *et al*., 2001; Kelly and Garavan, 2005). Hence, participants were scanned twice prior to training (Pre-training 1, Pre-training 2) and once after training (Post-training). Participants received no training between the first two scans to measure repetition effects. After the second scan, participants underwent 12-h memory training during which they learned different mnemonic procedures to support verbal memory. This protocol allowed for examination of the effect of repetition on brain activation by comparing Pre-training 1 with Pre-training 2. Additionally, in the event that repetition had an impact on the memory-related brain activations, comparing Post-training with Pre-training 2 would indicate the activation changes that were specific to training over and above this repetition effect. Our primary behavioural-outcome measure was word recall, an experimental task that was amenable to the techniques taught during training.

The objectives of the study were to identify the brain network associated with memory training in MCI and assess: (i) whether the network comprised regions involved prior to training or new alternative ones; (ii) whether those regions reflect successful compensation; (iii) whether the pattern of changes is similar to or different from that found in healthy older adults; and (iv) whether training in subjects with MCI normalized their brain activation relative to healthy older adults.

Materials and methods

Participants

This study included 30 participants: 15 subjects with MCI and 15 matched healthy older adults. Subjects with MCI were recruited from memory clinics in Montreal and met criteria for single domain or multiple domain amnestic MCI (Petersen et al., 2001). These criteria include the presence of a memory complaint corroborated by an informant when possible, a performance of at least 1.5 SD below the mean of age-standardized norms on memory tests (single domain amnestic MCI) or on memory tests and those measuring other cognitive functions (multiple domain amnestic MCI), the absence of dementia on the basis of clinical evaluation and clinical judgement, normal score on the Mini-Mental State examination (adjusted for age and education); and the absence of a significant impact on functional independence. Healthy older adults were recruited from the same community as the individuals with MCI.

All participants were right handed and francophone and showed normal or corrected vision and hearing. All participants underwent a clinical and neuropsychological assessment. Exclusion criteria included probable or possible Alzheimer's disease based on the NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association) (McKhann et al., 1984) and DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th edition) (American Psychiatric Association, 2000) criteria; other forms of dementia; presence or history of severe psychiatric disorder, cerebrovascular disease, neurological disorder or alcoholism; general anaesthesia in the previous 6 months; use of psychotropic medication; and presence of MRI exclusion conditions. None of the healthy controls met criteria for MCI. The study was approved by the Regroupement neuroimagerie, Quebec's research ethics board (CMER-RNQ).

Memory training

Episodic memory training was administered during six weekly sessions of ~120 min each, using a programme that has been shown to improve memory in subjects with MCI and healthy older adults (Belleville et al., 2006). Training was provided in small groups (4–5 participants per group) by experienced clinical neuropsychologists blinded to pre-training results. Participants learned different mnemonics and techniques to promote elaborate encoding and retrieval. Participants were provided with psychoeducational information regarding memory and ageing and were then trained with interactive imagery, the method of loci, face-name associations, hierarchical organization and semantic organization techniques.

Cognitive outcome memory measure

Participants were asked to study two lists of 12 frequent and concrete words taken from the Côte-des-Neiges Computerized Memory Battery (Belleville et al., 2002). Words were presented visually, and free recall was measured in an immediate recall condition and a 10 min delayed recall condition. An experimenter administered the task 1 week prior to training and 1 week following training using alternate versions.

Neuroimaging measures

Brain activation related to memory encoding was measured with six lists of eight concrete words, 1–3 syllables in length (4 s presentation rate, 1 s interstimulus interval). Items were presented visually with E-Prime, and participants were instructed to read silently and memorize the words. In the encoding-control condition, pseudo-words matched to the words in terms of length, vowel/consonant ratio and phonological complexity were shown with the same temporal parameters as those in the memory encoding condition. Participants were instructed to read the pseudo-words covertly. To measure activation during retrieval, six lists of words were presented (4 s presentation rate, 1 s inter stimulus interval), half of which had been studied during encoding and half of which were new words similar to the encoding words in terms of length, frequency and concreteness. Participants were asked to indicate whether they had seen the word in the study phase by pressing the appropriate key of a two-button response box. In the retrieval-control condition, participants were instructed to read a series of new pseudo-words covertly and to press one of the two buttons of the same response box randomly.

Two runs were conducted, one for encoding and one for retrieval. Each run included six blocks of rest (28 s), six blocks of the control condition (30 s) and six blocks of the memory condition (40 s). Brief instructions (4 s), modelled as a condition of no interest, were presented prior to each block (Clement and Belleville, 2009; Clement et al., 2010). The same procedure was conducted 6 weeks prior to training (Pre-training 1), 1 week prior to training (Pre-training 2) and 1 week after training (Post-training). Participants underwent cognitive training between the second and the third functional MRI scanning sessions (Pre-training 2 and Post-training). Parallel versions of the memory lists, matched for word frequency, semantic category and concreteness, were used for each time measure and counterbalanced across subjects. Prior to the session, participants were familiarized with the entire functional MRI procedure using a simulator. The experimenter involved in the pre–post measurement was blinded to both the participants' clinical group and the research hypotheses in relation to treatment effects.

Data acquisition

MRI was performed using a Siemens 3 T MAGNETOM Trio System (Erlangen, Germany) at the Unité de Neuroimagerie Fonctionnelle of the Institut universitaire de gériatrie de Montréal. Functional MRIs were acquired using gradient-echo echo-planar imaging sequences (GE-EPI) sensitive to blood oxygen level-dependent contrast (repetition time/echo time = 2000/30 ms, flip angle = 90°, 31 interleaved slices, voxel size = $3.75 \times 3.75 \times 5$ mm^3 with a gap of 1 mm, field of view = 240 mm, matrix = 64×64). A 3D structural image was taken at the end of the two runs using a sagittal T_1-weighted 3D MPRAGE sequence (repetition time/echo time = 1950/3.93 ms, flip angle = 15°; 176 slices, voxel size = $1 \times 1 \times 1$ mm^3, field of view = 256 mm, matrix = 256×256).

Image processing and data analysis

Data were analysed in MATLAB 7.3 (http://www.mathworks.com) using the statistical parametric mapping software SPM2 (http://www.fil.ion.ucl.ac.uk/spm/). The first three volumes were automatically discarded to allow the magnetization to reach equilibrium. The remaining images were first converted into Analyse format and unwarped. Functional volumes of each subject were then realigned to the first acquired volume in the session, and a mean realigned volume was created for each participant. The realigned volumes were spatially normalized into Montréal Neurological Institute stereotaxic space and spatially smoothed with an 8-mm Gaussian kernel. In the first-level analysis, the coefficients for each contrast were estimated separately in fixed effect models for each participant. A random effects (RFX) analysis was then performed by calculating two one-way analyses of variance (ANOVAs) with four groups (healthy controls pre-training, healthy controls post-training, MCI pre-training, MCI post-training), one for encoding and one for retrieval. An uncorrected threshold of $P < 0.001$ with 10 contiguous voxels was used for both the within-subject and between-subject comparisons. Region-of-interest images of the areas showing significantly more/less activation in individuals with MCI than in healthy controls in pre-training or significantly more/less activation in pre-training than in post-training were created with MarsBaR (Brett *et al.*, 2002), and the average beta values of these region of interests were extracted for each group and for each condition during both sessions. Two-way ANOVAs were computed in Statistical Package for the Social Sciences 13.0 (http://www.spss.com) for regions that showed group differences in activation at pre-training in order to assess whether training would reduce these group differences. Correlations were then computed between these regions and the performances of the subjects during pre- and post-training. Finally, given the critical implications of the hippocampus in both memory and Alzheimer's disease, we complemented all of our analyses using this structure as a region of interest. We created a region of interest image of the right and left hippocampi with the Wake Forest University PickAtlas (Maldjian *et al.*, 2003). Following initial whole-brain analyses, the pre-training within- and between-group comparisons and the post-training effects were analysed again on this region of interest with a less stringent threshold ($P < 0.01$ uncorrected, with 10 contiguous voxels).

Results

Clinical and cognitive results

Table 1 presents the demographical and clinical characteristics of the MCI participants and healthy older adults. The ages and educational levels of the two groups were comparable. As expected, subjects with MCI showed mild cognitive deficits relative to healthy controls, particularly in the domain of memory. Table 2 presents the data obtained just prior and after training for subjects with MCI and healthy controls on the immediate and delayed recall of the 12-word lists used as a cognitive outcome measure. A two (Group) × two (Intervention) × two (Delay) ANOVA indicated a significant intervention effect, $F(1,28) = 7.441$, $P < 0.05$ ($\eta^2 = 0.21$, power = 0.75), as both groups improved their recall

Table 1 Clinical characteristics of subjects with MCI and healthy controls (SD)

	MCI	Healthy controls
Age	70.13 (7.34)	70 (7.26)
Sex	11F 4M	10F 5M
Education	13.73 (4.33)	13.4 (3.10)
MMSE (/30)	27.73 (1.87)**	29.1 (0.74)
MDRS (/144)	133.33 (7.85)***	140.8 (2.98)
RL/RI delayed free recall (/16)	8.40 (3.81)***	13.4 (1.59)
RL/RI delayed cued recall (/16)	13.53 (3.81)*	15.73 (0.80)
Paragraph immediate recall (BEM)	7.13 (1.68)	8.5 (1.90)
Paragraph delayed recall (BEM)	6.08 (1.65)***	8.72 (1.75)
Digit symbol (WAIS) (scaled score)	9.07 (2.58)*	12.4 (1.9)
Stroop (time on third plate)	37.84 (15.78)*	23.49 (5.54)
Rey figure (copy)	27.77 (4.8)	30.25 (5.57)

Significance of the difference between MCI and healthy older adults at *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.
BEM = *Batterie d'efficience mnésique*; F = female; M = male; MDRS = Mattis Dementia Rating Scale; MMSE = Mini-Mental State Examination; RL/RI = *Rappel libre/rappel indicé* (Free/Clued recall); WAIS = Wechsler Adult Intelligence Scale.

Table 2 Performance on the memory outcome measure before training and after training

	MCI		Healthy controls	
	Pre-training 2	Post-training	Pre-training 2	Post-training
Immediate word recall (/12)*	6.5 (2.7)	7.1 (3.5)	8.3 (2.2)	9.3 (1.8)
Delayed word recall (/12)*	4.0 (3.4)	5.3 (4.1)	6.9 (3.0)	7.6 (2.4)
Performance in the scan*	62.35 (7.59)	70.83 (3.36)	74.52 (3.10)	82.21 (3.44)

*Significant training effect at $P < 0.01$.

after training. There was also a significant Delay effect, $F(1, 28) = 76.523$, $P < 0.001$ ($\eta^2 = 0.73$, power = 1.00), due to better performance on the immediate compared with the delayed recall. As expected, the Group effect was also significant, $F(1, 28) = 5.31$, $P < 0.05$ ($\eta^2 = 0.16$, power = 0.605), as subjects with MCI recalled fewer words than healthy older adults. None of the interactions involving the Group and Intervention factors reached significance. To complement the behavioural analysis, we assessed percent correct recognition in the scan for the Pre-training 1, Pre-training 2 and Post-training sessions using a two (Group) × three (Session) ANOVA (the data for one individual with MCI and two healthy older adults were not included in the

Figure 1 Performance in the scan prior to and after training.

analysis because of technical problems with response recording during Pre-training 1). Results indicated a significant Session effect, $F(2, 50) = 7.323$, $P < 0.01$ ($\eta^2 = 0.23$, power = 0.92). Figure 1 shows that performance after training was better than before training, but the only significant comparison was that between Post-training and Pre-training 1. The main Group effect was also significant, $F(1, 25) = 4.609$, $P < 0.05$ ($\eta^2 = 0.16$, power = 0.54). There was no Group × Session interaction ($F < 1$).

Brain activation related to task repetition without training

The functional MRI repetition effect on brain activation was measured by comparing the activation in Pre-training Session 1 with that in Pre-training Session 2. Comparisons were performed separately for healthy older adults and subjects with MCI and for encoding and retrieval (Table 3). In healthy controls, a few small areas showed less activation during Pre-training 2 than during Pre-training 1, and these areas were located in the right superior temporal gyrus and prefrontal cortex during encoding. Subjects with MCI also showed areas of decreased activation during encoding in the prefrontal cortex, cingulate gyrus and right inferior parietal gyrus. They also showed increased activation in the right basal ganglia and cerebellum during encoding and in the right caudate, cerebellum and inferior parietal lobule at retrieval. Thus, repeating the memory task without training resulted in a small but
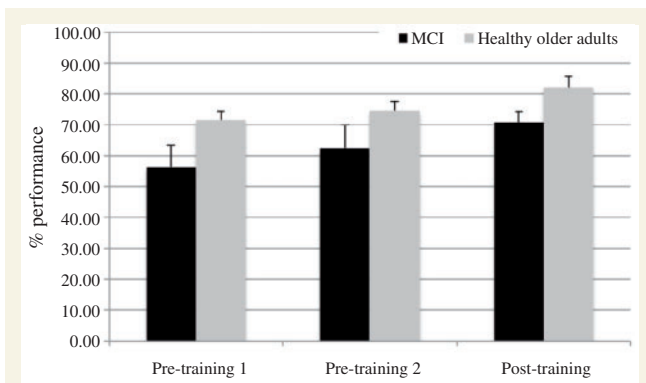
Table 3 Clusters (>10 voxels) showing activation differences when comparing Pre-training 1 and Pre-training 2 during encoding and retrieval in healthy controls and subjects with MCI

Region (Brodmann area)	MNI coordinates			Cluster size	t-value
	X	Y	Z		
Healthy controls					
Retrieval: Pre-training 1 > Pre-training 2					
Right superior temporal gyrus and precentral gyrus (6, 22, 42, 43)	60	−8	10	48	3.96
Right inferior frontal gyrus (44)	56	6	22	13	3.67
Left medial frontal gyrus (9)	−4	50	22	11	3.63
Left insula and inferior frontal gyrus (47)	−46	16	2	12	3.56
MCI					
Encoding: Pre-training 1 > Pre-training 2					
Right supramarginal gyrus and inferior parietal gyrus (40)	58	−38	42	259	5.17
Left middle frontal gyrus (8)	−22	22	42	95	4.33
Left middle/right anterior cingulate and frontal gyrus (10, 11, 24, 32, 47)	−20	34	−8	635	4.30
	12	42	−4		4.15
Left anterior cingulate (32)	−8	36	14	33	4.03
Right medial frontal gyrus (6)	12	6	56	20	3.86
Right postcentral gyrus (1, 2)	56	−22	48	21	3.76
Encoding: Pre-training 2 > Pre-training 1					
Right cerebellum	0	−40	−10	20	3.98
Left insula (13)	−40	−16	8	19	3.85
Right substantia nigra	16	−20	−12	21	3.74
Right globus pallidus and putamen	24	−12	−4	21	3.62
Retrieval: Pre-training 2 > Pre-training 1					
Right cingulate gyrus and caudate	14	−8	26	44	3.96
Right inferior parietal lobe (7)	30	−58	44	15	3.51
Right cerebellum	36	−72	−36	16	3.51

Table 4 Brain activation before training (Pre-training 2) in healthy controls: activated clusters for memory encoding and memory retrieval ($P < 0.001$; >10 voxels)

Region (Brodmann area)	MNI coordinates			Cluster size	t-value
	X	Y	Z		
Memory encoding > control (pseudowords)					
Left/right insula, middle and medial frontal gyrus, cingulate gyrus and precentral gyrus (6, 9, 10, 13, 22, 24, 32)	12	16	40	16 475	6.93
Left precentral and postcentral gyrus (3, 4)	−22	−20	54	354	4.24
Left inferior parietal lobule (40)	−56	−50	30	19	3.75
Right inferior frontal gyrus (44, 45)	54	14	12	16	3.65
Left inferior parietal lobule (40)	−24	−44	56	19	3.56
Left insula	−50	−40	20	13	3.54
Right precentral and postcentral gyrus (3, 4)	26	−30	58	21	3.45
Memory retrieval > control (pseudoword)					
Left/right medial and superior frontal, and cingulate gyri (6, 8, 9, 24, 32)	10	18	40	2182	6.78
	−5	22	44		5.09
Left insula and inferior frontal gyrus (13, 45, 47)	−30	20	2	436	5.50
Right inferior and middle frontal gyrus (10)	36	46	6	89	4.97
Right thalamus and caudate nucleus	12	0	8	123	4.83
Right insula and inferior frontal gyrus (13, 45, 47)	36	24	2	263	4.78
Left inferior and middle frontal gyrus (10)	−40	48	−2	55	4.47
Left inferior frontal gyrus (9)	−44	18	32	40	3.97
Left thalamus and caudate nucleus	−12	0	12	90	3.53

measurable effect on brain activation and, in most cases, produced a reduction in brain activation.

Brain activation related to memory

To support the interpretation of the training-related changes and, more precisely, to determine if training resulted in the activation of either new brain areas or areas that were already activated prior to training, we first assessed the areas of activation prior to training (Pre-training 2) in healthy older adults and subjects with MCI. During encoding, healthy older adults (Table 4) showed activation in a number of regions known for their implication in verbal episodic memory and verbal processing (Cabeza and Nyberg, 2000). These regions included a large bilateral cluster implicating the middle and medial frontal gyrus and the anterior cingulate, two clusters in the left inferior parietal lobule (Brodmann area 40), and one cluster in the right inferior frontal gyrus (Brodmann areas 44 and 45). Subjects with MCI (Table 5) also showed activation of a bilateral network during encoding that included the caudate nucleus, the anterior cingulate bilaterally, the right medial frontal gyrus (Brodmann areas 9 and 32), the left precuneus and the left frontal gyrus (Brodmann area 13). During retrieval, healthy older adults and subjects with MCI showed activation in a large number of regions, again in both the right and left hemispheres, particularly in the prefrontal cortex, cingulate gyrus, basal ganglia, left hippocampus and left parietal lobe. Many of these areas are typically involved in episodic memory, including the inferior prefrontal cortex, cingulate and hippocampus. The region of interest analyses revealed significant activation of the right (cluster size: 83; t-value: 3.16) and left hippocampi (cluster size: 24; t-value: 3.04) during encoding in

healthy older adults. The region of interest analyses also revealed that subjects with MCI showed activation of the right (cluster size: 13; t-value: 3.57) and left hippocampi (cluster size: 32; t-value: 3.55) during encoding. Subjects with MCI also activated the right (cluster size: 10; t-value: 2.7) and left hippocampi (cluster size: 38; t-value: 3.64) during retrieval.

Brain activation related to mild cognitive impairment

We compared the areas of activation that differed between the two groups prior to training (Table 6). During encoding, subjects with MCI showed less activation than healthy older adults in the cingulate gyrus and medial frontal gyrus (Brodmann areas 24 and 32) bilaterally, in the right superior and medial frontal gyrus (Brodmann area 10) and in the right inferior parietal lobule (Brodmann area 40), but a small cluster of the right inferior frontal gyrus (Brodmann area 47) showed more activation in subjects with MCI than healthy older adults. During retrieval, subjects with MCI showed less activation than healthy older adults in the left middle frontal gyrus (Brodmann area 10) and more activation than healthy older adults in the right superior parietal lobule (Brodmann area 7). The use of region of interest analyses showed no significant group differences in the activation of the hippocampus.

Brain activation related to training

The effect of training on brain activation was measured by comparing activation prior to training (Pre-training 2) with that after training (Post-training). During encoding, healthy older adults

Table 5 Brain activation before training (Pre-training 2) in subjects with MCI: activated clusters for memory encoding and memory retrieval (*P* < 0.001; >10 voxels)

Region (Brodmann area)	MNI coordinates			Cluster size	t-value
	X	Y	Z		
Memory encoding > Control (pseudowords)					
Left insula and precentral gyrus (13, 6)	−44	−14	6	58	4.54
Left/right caudate nucleus and anterior cingulate	6	18	18	192	4.54
	−4	20	16		3.90
Left precuneus (7)	−6	−62	50	26	3.89
Right medial frontal gyrus and anterior cingulate gyrus (9, 32)	14	38	22	23	3.85
Left cingulate gyrus (24, 33)	10	6	30	24	3.75
Left frontal gyrus and insula (13)	−32	22	14	14	3.66
Memory retrieval > Control (pseudoword)					
Left/right medial and superior frontal, and cingulate gyri	−6	22	32	1687	5.32
(6, 8, 9, 24, 32, 33)	10	30	22		4.77
Left/right thalamus, caudate, putamen nucleus and globus pallidus and left insula and inferior frontal gyrus (13, 47)	−22	8	16	2039	5.13
Left inferior and superior parietal lobule and precuneus (7, 39, 40)	−32	−72	42	296	4.99
Right insula and inferior frontal gyrus (13, 45, 47)	36	22	−6	436	4.86
Left cingulate gyrus (23, 24, 31)	−6	−36	36	91	4.17
Left hippocampus	−32	−34	−8	11	3.64
Right angular gyrus (39)	36	−64	36	22	3.63

Table 6 Clusters (>10 voxels) in which subjects with MCI differed from healthy controls prior to training (Pre-training 2; *P* < 0.001; >10 voxels)

Region (Brodmann area)	MNI coordinates			Cluster size	t-value
	X	Y	Z		
Encoding					
Healthy controls > MCI					
Left/right cingulate gyrus and medial frontal gyrus (24, 32)	12	16	40	189	4.36
Right superior and medial frontal gyrus (10)	20	54	18	88	4.04
Right inferior parietal lobule (40)	58	−40	42	23	3.90
MCI > healthy controls					
Right inferior frontal gyrus (47)	36	20	−12	14	3.89
Retrieval					
Healthy controls > MCI					
Left middle frontal gyrus (10)	−44	48	0	11	3.53
MCI > healthy controls					
Right superior parietal lobule (7)	20	−68	52	45	3.87

(Table 7) showed only reduced activation after training. Areas of reduced activation were found in a network that included the basal ganglia bilaterally, the cingulate gyrus bilaterally, the right inferior frontal gyrus (Brodmann areas 13 and 45), the right inferior (Brodmann areas 39 and 40) and superior parietal cortex (Brodmann area 7) and the right medial, inferior and superior frontal gyrus (Brodmann areas 9 and 45). Less activation was also found in the left prefrontal cortex (Brodmann areas 9, 10 and 32) and left precentral gyrus (Brodmann areas 13 and 44). The use of region of interest analyses revealed a significant training-related reduction in activation in the right hippocampus in healthy older adults during encoding (cluster size: 26; *t*-value: 2.80).

In contrast, retrieval was associated with increased activation after training in the right middle temporal gyrus (Brodmann area 21) and thalamus, the right superior temporal gyrus (Brodmann areas 6, 22 and 44), the right putamen and precuneus (Brodmann areas 43 and 7), the precuneus bilaterally (Brodmann area 7) and the left superior temporal and inferior frontal gyri (Brodmann areas 38, 45 and 47). The use of region of interest analyses indicated a significant training-related increase in activation in the right hippocampus in healthy older adults during retrieval (cluster size: 26; *t*-value: 3.35).

The same comparisons in subjects with MCI led to quite different findings (Table 8 and Fig. 2). Comparing brain activation associated with encoding before and after training indicated greater

Table 7 Clusters (>10 voxels) for which healthy controls showed differences in activation between Pre-training 2 and Post-training

Region (Brodmann area)	MNI coordinates			Cluster size	*t*-value
	X	Y	Z		
Encoding					
Pre-training 2 > Post-training					
Right insula (13) and right putamen	30	−4	20	495	4.68
Left insula (13) and caudate	−24	−24	20	262	4.82
Left putamen, lateral globus pallidus and ventral posterior lateral nucleus	−30	−22	0	71	4.79
Right inferior parietal gyrus, supramarginal gyrus (40), cingulate gyrus (24) and caudate	24	−32	24	902	4.54
Right inferior frontal gyrus (45)	42	30	8	271	4.45
Left/right caudate	8	10	14	924	4.42
	−12	14	14		4.33
Right supramarginal gyrus and superior temporal gyrus (39, 40)	60	−54	28	28	4.14
Right precentral gyrus (44)	44	4	12	26	3.97
Left medial and superior frontal gyrus and anterior cingulate (9, 10, 32)	−10	48	22	96	3.96
Right medial and superior frontal gyrus (9)	14	44	24	110	3.93
Right middle frontal gyrus (9)	36	12	40	32	3.81
Right cingulate gyrus (24, 32)	14	4	46	37	3.76
Right precuneus and cingulate gyrus (7, 31)	14	−48	42	55	3.51
Retrieval					
Post-training > Pre-training 2					
Right middle temporal gyrus (21)	40	−6	−10	26	3.67
Right thalamus	10	−24	8	25	3.66
Left superior temporal gyrus and inferior frontal gyrus (38, 47)	−46	16	−8	20	3.58
Left inferior frontal gyrus (45, 47)	−50	24	4	23	3.49
Right superior temporal gyrus and precentral gyrus (6, 22, 44)	62	4	8	23	3.47
Right precuneus (7)	8	−54	62	18	3.46
Right postcentral gyrus (43)	64	−16	18	13	3.46
Right putamen	28	−2	4	12	3.43
Left precuneus (7)	−4	−70	48	12	3.36

activation after training in the left superior temporal gyrus (Brodmann areas 13, 21 and 22); the left thalamus, putamen and globus pallidus; the right inferior parietal cortex (Brodmann area 40); the right superior frontal gyrus (Brodmann area 6); and the right cerebellum. During retrieval, more activation was also found after training than before in a number of brain areas including the left post-central gyrus and inferior parietal lobule (Brodmann areas 1, 2, 3 and 40), the left inferior and supramarginal gyrus (Brodmann areas 39 and 40), the posterior cingulate bilaterally (Brodmann area 29), the left and right superior temporal gyri (Brodmann areas 22 and 38), the right insula and the left middle frontal gyrus (Brodmann area 6). The use of region of interest analyses revealed no training-related changes in the hippocampus in individuals with MCI.

Training effect on activation related to mild cognitive impairment

The areas of impairment in MCI reported in Table 6 were used as functional region of interests to determine if there was a Group × Time interaction. This analysis tested whether brain differences found prior to training would be reduced by the intervention. We found a significant Group × Time interaction during encoding for a cluster located in the cingulate and medial frontal gyri (Brodmann areas 24 and 32), $F(1, 28) = 9.071$, $P < 0.01$, and in the right inferior parietal lobule (Brodmann area 40), $F(1, 28) = 26.636$, $P < 0.001$. For retrieval, we found a Group × Time interaction for the left middle frontal gyrus (Brodmann area 10), $F(1, 28) = 8.804$, $P < 0.01$, and right superior parietal lobule (Brodmann area 7), $F(1, 28) = 4.913$, $P < 0.05$. For regions where an interaction was reported, the Group difference observed prior to training was either attenuated or no longer seen after training (Supplementary Fig. 3).

Correlation between performance and training-related activation

Correlational analyses were used to assess whether the brain changes that occurred between the pre- and post-training scans were associated with better performance on the behavioural memory task. Word recall at post-training was thus correlated with changes in activation in brain regions found to be modified by the intervention. In healthy older adults, a positive correlation was found between immediate word recall and post-training activation during retrieval in the left inferior frontal gyrus (Brodmann areas 45 and 47; $r = 0.512$; $P = 0.05$). In subjects with MCI, the

Table 8 Clusters (>10 voxels) for which subjects with MCIs showed differences in activation between Pre-training 2 and Post-training

Region (Brodmann area)	MNI coordinates			Cluster size	t-value
	X	Y	Z		
Encoding					
Post-training > Pre-training 2					
Left superior temporal gyrus and insula (13, 21, 22)	−40	−18	−12	102	4.69
Left thalamus, putamen and globus pallidus	−12	−22	0	151	4.51
Right inferior parietal lobule (40)	60	−40	42	57	4.41
Right superior frontal gyrus (6)	22	−24	76	71	4.22
Right cerebellum	24	−52	−18	16	4.14
Retrieval					
Post-training > Pre-training 2					
Left postcentral gyrus, and inferior parietal lobule (1, 2, 3, 40)	−46	−36	62	259	4.92
Left inferior parietal lobule (39, 40)	−60	−52	38	43	4.10
Left/right posterior cingulate (29)	−4	−46	0	41	3.78
Left superior temporal gyrus (22, 38)	−46	8	−6	13	3.76
Right insula (13)	40	2	−4	12	3.69
Right superior temporal gyrus (22)	60	2	4	23	3.63
Left precuneus (7)	−24	−54	70	15	3.53
Left middle frontal gyrus (6)	−38	−8	64	12	3.53
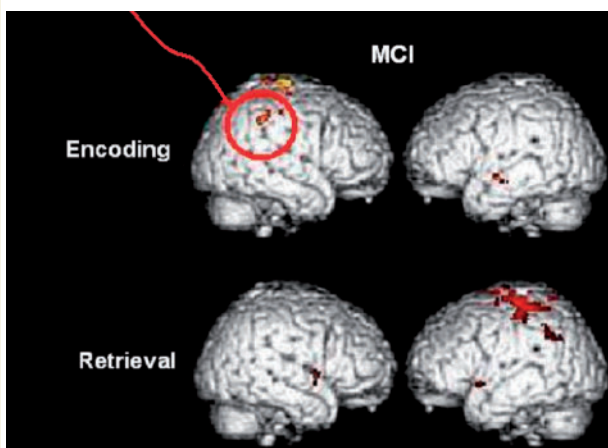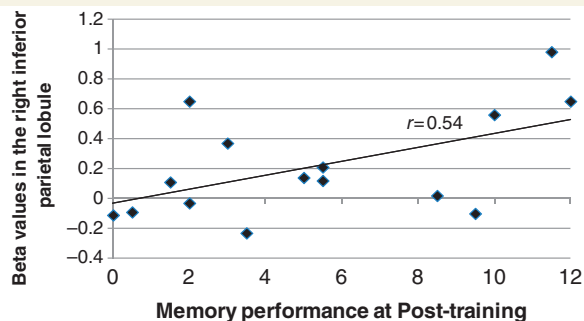
Figure 2 Areas of increased brain activation after training in the MCI group: activated clusters (Post-training > Pre-training 2) for both memory encoding and retrieval ($P < 0.001$; >10 voxels). A scatter plot with fit line shows the significant correlations in subjects with MCI between their memory performances at post-training and the β-values for the encoding condition at post-training in the right inferior parietal lobule.

correlation was significant between delayed word recall and activation during encoding for the right inferior parietal lobule (Brodmann area 40; $r = 0.538$; $P < 0.05$; Fig. 2). Importantly, no correlation was found between memory performance and activation of this area prior to training ($r = 0.12$, not significant).

Discussion

Prior to training, healthy older adults and subjects with MCI showed activation in a number of frontal and parietal regions within a bilateral network typically involved in memory. Furthermore, the region of interest analyses indicated that both groups activated the hippocampus bilaterally during encoding prior to training.

In subjects with MCI, training resulted in a large network of increased brain activation. During encoding, greater activation was found in the right inferior parietal lobule and frontal gyrus. Regions implicated in procedural memory (Doyon and Benali, 2005) also showed increased activation as a result of training (right cerebellum and left basal ganglia). During retrieval, training increased activation in regions of the left parietal and prefrontal cortex and the superior temporal gyrus bilaterally. There are many reasons to believe that these changes are not related to the mere repetition of the functional MRI memory scanning procedure. First, after the procedure was repeated twice prior to memory intervention, we found mostly areas of reduced brain activation. This finding is consistent with previously published data on test–retest reliability of functional MRI activations in MCI (Clement and Belleville, 2009). It is also consistent with data for younger adults that indicate that repeating a task is associated with a reduction in brain activation (Kelly and Garavan, 2005). This tendency could be

due in part to neural facilitation and/or to participants becoming more familiar and comfortable with the scanning environment and task situation with repetition.

For the most part, training-related brain changes involved the activation of new alternative brain areas in subjects with MCI, that is, areas that were not recruited during the memory task prior to training (e.g. the right parietal cortex for encoding and the superior temporal gyrus for retrieval). During retrieval, we found a few areas with accumulated activation; that is, activation within regions that were already active prior to the intervention (e.g. the left inferior parietal lobule). This finding agrees with models of brain compensation in ageing and suggests that maintaining optimal memory functions relies on both increased activation of specialized areas and recruitment of new alternative brain networks (Cabeza, 2002; Reuter-Lorenz, 2002; Stern *et al.*, 2005). Interestingly, many of the newly activated areas have been associated with semantic elaboration or visuospatial memory, which is consistent with the mnemonics that the participants learned (Cabeza and Nyberg, 2000).

The new areas of activation are typically involved in language processing (left temporal lobe), spatial and object memory (right prefrontal and parietal areas) and skill learning (cerebellum and basal ganglia). Thus, the newly recruited brain regions are those involved in the types of strategies that participants learned to implement. Interestingly, our finding of increased activation in the cerebellum and basal ganglia suggests that the regions associated with procedural and skill learning might also play a role in more complex learning. At retrieval, changes in activation reflect a combination of alternative areas and the larger engagement of a specialized memory network.

Furthermore, except for the right inferior parietal lobule, all areas that showed increased activation after training in subjects with MCI were normal prior to training. This finding can be explained by the rationale underlying our training programme. As described earlier, the programme was meant to rely on processes that are still mostly unimpaired in subjects with MCI. Importantly, a positive correlation was found in subjects with MCI between activation of the right parietal lobe, a region involved in visuospatial memory and performance after but not before training. This correlation strengthens our contentions that new areas of activation reflect successful compensation and that improvement depends on the recruitment of those new areas.

During retrieval, training is associated with increased activation in healthy older adults as is the case for MCI. However, the training effects on brain activation in healthy older adults are strikingly different from those in subjects with MCI during encoding. Indeed, healthy controls showed reduced activation associated with encoding after intervention. These different findings have many possible causes. One possibility is that the healthy older adults were using active encoding strategies during pre-training and our intervention essentially allowed them to use these strategies more efficiently, hence the reduced activation during encoding. The activation changes found in the right hippocampus suggests that visuospatial encoding might represent one of these active encoding processes. It is also possible that, because they are more cognitively apt, healthy older adults had sufficient time to develop more expertise with the learned strategies than subjects

with MCI. Differences in activation may thus reflect the fact that the two groups lie on a different part of the learning spectrum. They certainly reflect the fact that equivalent increases in performance can arise from drastically different brain mechanisms.

By including healthy older adults in the study, we were able to assess whether training in MCI reversed group-related effects on brain activation. One important finding was that memory training normalizes the brain activation deficits associated with MCI. Prior to training, subjects with MCI showed less activation than healthy controls in a number of brain regions, which agrees with findings of consistent Alzheimer's disease-related increased activation of the frontal areas [particularly in the inferior region; see Schwindt and Black (2009) for a meta-analysis]. There are also consistent data indicating reduced activation in the medial portion of the brain (cingulate and medial frontal gyri), a region shown to be involved in control processes (Celone *et al.*, 2006; Schwindt and Black, 2009). We have also reported increased prefrontal activation associated with memory encoding in MCI (Clement and Belleville, 2009; Clement *et al.*, 2010) and have suggested that this may play a compensatory role at the beginning of the disease when symptoms are mild (Clement and Belleville, in press). Significant Group × Session interactions indicated that many of the activation differences between subjects with MCI and healthy older adults were attenuated by training. Notably, training diminished the group differences found in the cingulate/medial frontal gyrus and in the right parietal lobe. As these regions are involved in controlled processes and memory, this reduction may reflect the reinstatement of a typical active encoding as the memory task is completed.

There are many important questions that remain to be addressed, including how and whether these short training regimens merge with real life. Previous studies have found that training programmes that improve memory also have beneficial impact on well-being and on the subjective rating of memory functioning (Belleville *et al.*, 2006). Other studies have reported that training in reasoning can be effective in delaying decline in the functional capacities of healthy older adults over a 5-year period (Willis *et al.*, 2006). However, more work is needed to appraise the transfer from measures in the laboratory to measures in real life. Brain imaging can contribute to this effort by identifying the brain regions that are sensitive to training and that can be used to predict the tasks for which training is likely to be transferable (Lustig *et al.*, 2009). Another important issue is whether the brain changes found here are specific to this particular training programme or if they would be observed with any type of intense training as our design did not include an active control condition. Interestingly, however, the brain activation data are extremely coherent with the intervention format; increased activations were found in the brain areas related to the taught intervention, and the brain areas that correlate with improved performance are those most clearly associated with the content of the intervention (particularly the right Brodmann area 40, which is involved in visual memory).

This study has limitations that should be acknowledged. First, because it was intended to assess the brain imaging correlates of memory training, it was not designed as a randomized controlled trial to test the efficacy of the programme. The two pre-training

scans controlled for repetition effects in the MRI, as we wanted to distinguish brain changes related to repetition from those associated with the training, and the cognitive measures were not carried out in Pre-training session 1. However, a number of reasons support our belief that the improvement in the cognitive outcome is not related to a mere test–retest effect. First, the performance data during scanning indicate a significant time effect, and Fig. 1 shows that the increase in performance is smaller when Pre-training session 1 is compared with Pre-training session 2 than when either pre-training session is compared with Post-training. Second, we used alternative versions of the task for the Pre-training 2 and Post-training measures to ensure that participants did not show memory improvement as a result of repeating the same list. Finally, previous studies that used a similar training and testing protocol with MCI showed a 5–14% decrease in recall at retest in a wait-list condition (Belleville *et al.*, 2006). All of these elements provide support for an effect that goes beyond a simple test–retest effect.

Another limitation is the lack of a placebo-control condition. Use of placebo as a control condition is optimal for a clinical trial. However, a repeated design where participants are used as their own controls is not easily amenable to being placebo controlled because it would require that the placebo-controlled participants also complete two pre-training sessions, which would result in the statistical model for testing the specific effect of the training being extremely complex. Despite this limitation, our use of a repeated design was justified by a number of reasons: (i) it reduces the effect of scan repetition on brain activations at the individual level (which cannot be done in a randomized design) and thus provides a clearer picture of what is actually changed by the intervention (by removing brain changes related to the reduced stress or arousal experienced by subjects during the scanning process); (ii) it brings more power to the experiment by reducing the impact of inter-individual variability; and (iii) it circumvents the difficulty of finding a proper sham intervention, one that elicits completely different brain processes. We are comforted by the fact that increased activations were found in the brain areas related to the taught intervention, and that brain areas that correlate with improved performance are those most clearly associated with the content of the intervention.

In conclusion, this neuroimaging study indicates that the older brain is highly plastic and remains so even when suffering from the early effects of neurodegenerative diseases. When older adults with very early Alzheimer's disease are taught alternative strategies, their brains remain able to recruit new neural circuits to perform demanding memory tasks. Our results provide important information regarding the circuits modified by cognitive training in subjects with MCI. Memory training in MCI results in marked changes in a large brain network that includes regions typically implicated in memory as well as in a new alternative brain network that relates to the taught mnemonics. These data indicate that brain imaging is sensitive to change and support its use as a valid outcome for therapeutic studies. They also provide empirical support for the use of cognitive training as a potential treatment for people with memory difficulties.

Supplementary material

Supplementary material is available at *Brain* online.

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