Increased biomagnetic activity in healthy elderly with subjective memory complaints

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Abstract

Objective: Subjective memory complaints (SMCs) are frequently reported by elderly people with or without objective cognitive impairment (OMI) as assessed by neuropsychological tests. We investigate whether SMCs are associated with altered brain biomagnetic patterns even in the absence of OMI.

Methods: We report spatio-temporal patterns of brain magnetic activity recorded with magnetoencephalography during a memory task in 51 elderly participants divided into the following groups: patients with mild cognitive impairment (MCI) with SMC and OMI, individuals with SMC but not OMI, and healthy controls without neither SMC nor OMI. Exclusion criteria for all three groups included a diagnosis of depression or any other psychiatric condition.

Results: No statistically significant differences were found between MCI patients and participants with SMC. However, the SMC showed higher activation, between 200 and 900 ms after stimulus onset, than the control group in posterior ventral regions and in the dorsal pathway. MCI patients showed higher activation than the control group in the posterior part of the ventral pathway.

Conclusions: These findings suggest that similar physiological mechanisms may underlie SMC and MCI, which could be two stages in a cognitive continuum.

Significance: MEG provide different neurophysiological profiles between SMC and control subjects.

1. Introduction

In recent years, there is increased interest in the early diagnosis of dementia as treatment is likely to have a better chance of success, before the severe biochemical and morphological alterations associated with the condition take place. Additionally, there is increased social awareness about the memory deficits associated with dementia. In fact, 17–57% of elderly people report subjective memory complaints (SMCs) (Ganguli et al., 2004; Jessen et al., 2007; Mitchell, 2008a). SMC may occur both in the absence and presence of verifiable cognitive dysfunction. Results from a meta-analysis indicate that SMC are present in 42.8% of patients with dementia, in 38.2% of those with mild cognitive impairment (MCI) and in 17.4% of healthy elderly controls (Mitchell, 2008a).

It is still unclear what the clinical significance of presenting SMC is. In some individuals it may be the result of progressive memory deficit associated with aging without indicating a neurological pathology. Associations with neuroticism, anxiety, psychological stress and depression have been reported (Mitchell, 2008a; Sinforiani et al., 2007). More generally, cognitive complaints have been identified as one of the possible criteria to diagnose amnestic MCI (Petersen, 2004) a condition associated with a high risk to develop of dementia. While some studies have found a relationship between subjective and objective memory complaints others have failed to do so (see Jonker et al. (2000) for a review). Furthermore, whether SMC can guide the early diagnosis of dementia is still a matter of debate (Glodzik-Sobanska et al., 2007; Jonker et al., 2000; Kim et al., 2006; Mitchell, 2008a).

Neuroimaging studies have attempted to provide an objective measure of cognitive complaints. Diminished hippocampus and
entorhinal cortex volumes (Jessen et al., 2006; van der Flier et al., 2004), reduced hippocampal metabolism (Mosconi et al., 2008) and subcortical parieto-occipital white matter lesions (Stenset et al., 2008) have been reported in patients with SMC. In contrast, studies with larger cohorts of SMC patients did not find evidence for medial temporal atrophy (Frisoni et al., 2009) or white matter changes (Miranda et al., 2008). To establish whether changes in neuroimaging signals reflect a neurological basis of SMC it is important to exclude psychiatric conditions such as depression as they can have an influence on results (Kyomen et al., 2007).

In this study, we compare the brain magnetic activity during a memory task in three groups of elderly people: volunteers with SMC, mild cognitive impairment (MCI) patients with objective memory impairment as determined by a neuropsychological test and healthy elderly participants. In contrast to previous studies, exclusion criteria included having any psychiatric condition or personality disorder that could confound result interpretation. Additionally, the existence of SMC was based on a structured questionnaire with more than 20 questions as opposed to a list of 2 or 3 questions as used in most previous studies. A previous behavioural study found that SMC and MCI patients had similar clinical characteristics (Vestberg et al., 2010). If SMC and MCI arise from similar neurophysiological changes we would expect brain activity profiles to be more similar between these two groups than when compared to healthy controls. In addition, we would expect differences between SMC and healthy controls to resemble those found between MCI and healthy controls (Dickerson et al., 2005; Maestu et al., 2008), with higher activation for the SMC group in brain regions related to recognition memory processes.

2. Methods

2.1. Participants

Fifty-one, right handed, elderly participants recruited from the Geriatric Unit of the “Hospital Universitario San Carlos Madrid” and the “Centro de Prevención del Deterioro Cognitivo, Ayuntamiento de Madrid”, participated in the study. Participants were divided into three groups based on their clinical profiles: 21 participants were considered as multi-domain MCI patients, 18 as elderly control participants and 12 as SMC participants.

The subjective memory complaints group was composed by 12 (nine women, average 72.5 years) elderly participants who came, on their own initiative, to the “Centro for the Prevention of Cognitive Decline” and reported experiencing memory deficits. This is a public health centre in Madrid (Spain) which runs memory training programs for both healthy elders and MCI patients. Participants for the SMC group were selected following the criteria proposed by Abdulrab and Heun (2008): (1) patient stating that their memory function has deteriorated compared to earlier stages in life; (2) time of onset being in adulthood; (3) providing a valid example; (4) memory deterioration confirmed by an informant (close relative or friend); and (5) normal objective memory performance. The assessment was based on structured interview and a neuropsychological assessment. To ensure that memory complaints were not caused by a psychiatric condition all patients were interviewed by an experienced psychiatrist (PM) and had to score below 9 in the geriatric depression scale (Yesavage, 1991). Additionally, to confirm the memory complaints, participants from this group had to score higher than 13 (mean 27.6) in the Memory Failures of Everyday (MFE) test (Sunderland et al., 1983). Given that the association between subjective ratings and future cognitive decline is stronger when complaints have been confirmed by an informant (Farias et al., 2005), we required confirmation from relatives or close friends. None of these patients met the criteria for MCI and had no history of psychiatric or neurological disorders. Most SMC patients were following educational courses at local social centres.

MCI diagnosis was established according to the criteria proposed by Petersen et al. (Grundman et al., 2004; Petersen, 2004). Thus, MCI patients fulfilled the following criteria: (1) cognitive complaint corroborated by an informant (a person who stays with the patient at least for half a day at least 4 days a week); (2) objective cognitive impairment, documented by delayed recall in the Logical Memory II subtest of the Revised Wechsler Memory Scale (score ≤16/50 for patients with more than 15 years of education; score ≤8/50 for patients with 8–15 years of education); (3) normal general cognitive function, as assessed by a clinician during a structured interview with the patient and an informant, and additionally a Mini Mental State Examination score greater than 24; (4) relatively preserved daily living activities as measured by the Lawton scale; and (5) not sufficiently impaired, cognitively and functionally to meet criteria for dementia. As a result 21 participants were included in the MCI group. Most SMC patients were following educational courses at local social centres. According to their clinical and neuropsychological profile, all patients in this group were considered multi-domain MCI patients (see Petersen (2004)). As for the geriatric depression scale, none of the MCI showed depression (score lower than 9) (Yesavage, 1991).

Eighteen healthy elderly participants were included as a control group. These participants were enrolled in educational courses at the Complutense University of Madrid. To confirm the absence of memory complaints a score of 0 was required in a 4-question questionnaire (see Mitchell (2008a)). None of the participants had a history of neurological or psychiatric condition.

To summarize, MCI patients showed both subjective and objective memory impairment. SMC subjects presented only with memory complaints with a normal score on the memory test and healthy elders showed neither subjective nor objective memory impairment.

MCI patients, SMC subjects and healthy participants underwent a neuropsychological assessment, in order to establish their cognitive status with respect to multiple cognitive functions. Specifically, memory impairment was assessed by the Logical Memory Test (immediate and delayed) from the Wechsler Memory Scale-III-R. Two scales of cognitive and functional status were applied as well: the Spanish version of the Mini Mental State Examination (MMSE) (Lobo et al., 1979), and the Global Deterioration Scale/Functional Assessment Staging GDS/FAST. Participants were selected so that the number of years of education (MCI patients: 8.5, SMC patients 8.3 and control participants 8.9 on average) and age was as similar as possible for the three groups. Table 1 presents demographic and clinical information for the three groups. It should be noted that even if subjects with SMCs did not fulfill criteria for MCI moderate differences in memory scores between the SMC and control group were present, as shown in the table. Before the MEG recording, all participants or their legal representatives gave written informed consent to participate in the study which was approved by the Local Ethics Committee.

2.2. Stimuli and task

MEG scans were obtained in the context of a modified version of the Sternberg’s letter-probe task (de Toledo-Morrell et al., 1991; Maestu et al., 2001) in which a set of five letters was presented and participants were asked to keep the letters in mind. After the presentation of the five-letter set, a series of single letters (500 ms in duration with a random ISI between 2 and 3 s) was introduced one at a time, and participants were asked to press a button with their right hand when a member of the previous set was detected. The list consisted of 250 letters in which half were targets (previously presented letters), and half distractors (not...
Previously presented letters. Participants undertook a training series before the actual test, which did not start until the participant demonstrated that he/she remembered the five-letter set. Letters were projected through a LCD video-projector (SONY VPL-X600E), situated outside the shielded-room onto a series of in-room mirrors, the last of which was suspended approximately 1 m above the participant’s face. Letters subtended 1.8° and 3° of horizontal and vertical visual angle, respectively.

2.3. MEG data collection and source analysis

The MEG signal was measured using a 148-channel whole-head magnetometer (MAGNES 2500 WH, 4-D Neuroimaging) confined in a magnetically-shielded room. Initially the raw data was baseline corrected on the basis of a prestimulus 100-ms window, and submitted to a noise reduction procedure which uses simultaneous recordings from nine reference channels. Thereafter, the signal was low-pass filtered at 30 Hz. Single trial epochs were visually inspected by an experienced investigator (FM). Epochs contaminated by ocular artifacts were corrected with an artifact-correction tool from the BESA® software package (http://www.besa.de/). Trials containing muscular artifacts were visually rejected. Artifact-free epochs from each channel were then averaged together selectively for the target condition. A minimum of 80 epochs were used to calculate the average signal for each condition.

A minimum norm estimation (MNE) procedure commonly used in MEG source reconstruction and described in detail elsewhere (Hämäläinen and Ilmoniemi, 1994; Hauk, 2004) was applied to estimate the cortical origin of the brain responses. The minimum-norm solution finds the distribution of sources that best explains the sensor data while having minimal power. Since cortical pyramidal neurons are believed to be the main contributors to the MEG signal the dipoles of the source space model were restricted to a cortical surface extracted from a structural MRI (Dale et al., 2000). A tessellated cortical mesh template surface derived from the Montreal Neurological Institute (MNI) phantom brain and implemented in SPM5 (www.fil.ion.ucl.ac.uk/spm/software/spm5/) served as a brain model to estimate the current source distribution. Typically, the dipoles of the distributed source model are evenly placed at each node of the mesh representing the white/grey matter interface. The SPM5 template we used contains 7204 dipole locations. This dipole mesh was used to calculate the forward solution using a spherical head model. As the magnetic field propagation is not distorted by the various tissue types of the head, a spherical head model is a good approximation to a realistic model in the case of MEG (Sarvas, 1987). The inverse solution (the estimation of the current source density based on the MEG topography) was calculated using the L2 minimum-norm solution (Hauk, 2004) using in-house MATLAB® code.

2.4. Statistical analysis

Nonparametric permutation testing (Holmes et al., 1996; Nichols and Holmes, 2002) was applied to find spatio-temporal clusters with significant differences between groups. In brief, a two-sample t-test between groups was performed for fixed dipole location and time sample. Neighbouring cells in space and time with a primary threshold \( p < 0.01 \) were clustered together. For each cluster the exceedance mass was calculated. The exceedance mass is defined as the sum of \( t \)-values in the cluster after subtracting the primary threshold. Next, surrogate \( t \)-maps were calculated by randomly dividing the participants from the two groups into surrogate groups matching the numbers in the original groups. Clusters for each surrogate map were also obtained. Five hundred surrogate maps were produced. From each of them the maximum and minimum cluster exceedance mass were included in the surrogate probability distribution. Thresholds were obtained from the 2.5th and 97.5th percentile of this distribution which ensures that there is only a 5% chance that one or more clusters from the original statistical map will present differences above threshold due to statistical fluctuations, and therefore corrects for multiple comparisons. The fieldtrip toolbox (Donders Institute for Brain, Cognition and Behaviour, Radboud University Nijmegen, The Netherlands http://www.ru.nl/neuroimaging/fieldtrip) was used for the statistical analysis. For visualization purposes a yellow circle marks maximum and minimum of statistical maps. A maximum of 5 maxima/minima per map are reported, no closer than 2 cm from each other and no less than 50% in amplitude with respect to the first maximum/minimum for that contrast. Figures show the average \( t \)-value over 100-ms windows of the thresholded \( t \)-maps.

3. Results

3.1. Behavioural data (MEG task)

No between-groups differences (\( t \)-test, \( p > 0.05 \) in all pair comparisons) were found in the number of letters correctly detected, although performance was lowest for the MCI group (Table 1).

3.2. MEG results

The comparison between the SMC and the MCI group did not show any significant differences in brain activity after correction for multiple comparisons. Although voxelwise uncorrected \( t \)-values were in the range \([-3.3:4.5] \) the cluster with the smallest corrected \( p \)-value had a \( p \)-value of \( p = 0.15 \).

The comparison between the SMC and the control group showed higher activation for the SMC group. Fig. 1 shows the average \( t \)-value of the thresholded \( t \)-maps after multiple comparison correction in 100 ms time windows. Thus, SMC patients showed higher activity than the control group in ventral posterior regions bilaterally (including the inferior parietal lobe, the temporal lobe and temporo-occipital regions) and the dorsal pathway bilaterally (including dorsal parietal cortex, motor/premotor cortex and dorsal prefrontal region) between 200 and 900 ms.

As expected (Maestu et al., 2008) the comparison between the MCI and the control group revealed, as well, higher activation for the MCI group, again between 200 and 900 ms. As in reference (Maestu et al., 2008) this higher activation was mainly concentrated in the ventral pathway (inferior parietal lobe), temporal lobe and ventral prefrontal region. In addition, we find increased activity in the dorsolateral prefrontal cortex, bilaterally, for late latency (Fig. 2), as described by the Talairach Daemon (Lancaster et al., 1997, 2000), for contrast maxima are reported in Table 2.

4. Discussion

The comparison between MCI patients, SMC individuals without psychiatric conditions and normal healthy elders affords a

<table>
<thead>
<tr>
<th>Age</th>
<th>MMSE</th>
<th>GDS</th>
<th>LM2</th>
<th>Hits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>72 ± 8</td>
<td>29.5 ± 0.7</td>
<td>1</td>
<td>27 ± 7</td>
</tr>
<tr>
<td>SMC</td>
<td>72 ± 6</td>
<td>28 ± 1</td>
<td>2</td>
<td>24 ± 10</td>
</tr>
<tr>
<td>MCI</td>
<td>75 ± 3</td>
<td>28 ± 1</td>
<td>3</td>
<td>14 ± 6</td>
</tr>
</tbody>
</table>
better understanding of the neural basis of memory complaints. Patients with memory complaints did not show significant differences in brain activity during the memory task in comparison with MCI patients that have both objective and subjective memory complaints. Thus, although cognitive tests differentiate between MCI and SMC subjects the MEG analysis did not yield any spatio-temporal significant differences between these two groups. This discrepancy suggests two possible scenarios: (1) SMC participants have a memory impairment not detected by the neuropsychological tests. (2) SMC and MCI have different aetiology but MEG is not sensitive enough to characterize the difference. Follow-up studies may clarify this issue. While there is still no consensus about the clinical significance of SMC the present result adds to the existing evidence suggesting that there are physiological differences between healthy elders and individuals reporting complaints. This notion is supported by the fact that the presence of subjective memory complaints in healthy elders increases the risk of future objective memory impairment, particularly when confirmed by an informant (Farias et al., 2005; Frerichs and Tuokko, 2006). Additionally, a recent meta-analysis indicates that, although the presence of SMC has a low value to diagnose cognitive impairment, its absence may be a reasonable method of excluding MCI (Mitchell, 2008b). It should be noted that the SMC patients included in this study, went on their own initiative to the health services, which indicates that there was a significant degree of concern about how their perceived memory deficits were affecting their daily lives. Furthermore, complaints were corroborated by an informant and psychiatric disorders were excluded. All these factors add reliability to the memory complaints, and further support the possibility that the lack of differences in brain activation between the MCI and SMC groups are a reflection of a common physiological deficit. However, the fact that these differences fail to reach a significance level suggests that they are not large enough to be above the statistical fluctuations that arise because of the sampling procedure. Even if differences between the SMC and MCI group turned out to be significant, for example in studies with larger groups, the fact that the difference between SMC patients and controls was much larger is likely to be preserved since the cluster with the smallest p-value in the SMC-control contrast had a p-value of p = 0.01, corrected, as compared to the p-value = 0.15 of the SMC-MCI contrast.

The comparison between the SMC group and controls provides the strongest argument in favour of the clinical significance of the biomagnetic data. The SMC group showed a time-modulated increase in activity in ventral posterior regions and in the dorsal pathway. Differences cannot be related to performance as both groups showed a high percentage of hits responses without significant differences between them. This profile of increased activity is similar to the previously reported comparison between MCI patients and healthy elderly controls (Dickerson et al., 2005; Maestu et al., 2008). In fact, the comparison between MCI and controls in this new sample showed increased activity in the MCI group in their daily lives.
ventral posterior regions. Activity in ventral posterior regions has been traditionally related with recognition memory tasks (see Simons et al. (2008)). Furthermore, these differences appear at similar latencies to those of the P3–N4–P6 event related components, which have been extensively related to declarative memory processes (Rugg and Yonelinas, 2003).

Additionally, SMC participants showed higher activation in the dorsal pathway, including the premotor and the dorsolateral prefrontal region. Activation of the dorsal pathway during working memory tasks has been previously reported (Campo et al., 2010). Bilateral activation in premotor regions has been related to articulatory rehearsal while maintaining information active in working memory (Maestu et al., 2001). The activation of the dorsolateral prefrontal region has been related to the manipulation of information in working memory (Van Hecke et al., 2010). These differences in brain activation between SMC patients and controls could be generally related to the use of a differential memory strategy (Maestu et al., 2003). It is of interest that differences were not limited to the dorsal pathway. The ventral pathway, formed by the ventral prefrontal region, the temporal lobe and the inferior parietal lobe, also showed increased activity in late latency windows in SMC patients as compared to controls. This increase in activity in the ventral pathway has been previously reported when comparing MCI patients and controls (Maestu et al., 2008) and in other brain pathologies such as patients with first episode schizophrenia (Tan et al., 2005). This activity increase in dorsal and ventral pathways in SMC patients could reflect a compensatory mechanism. The fact no differences between SMC and MCI patients were found in any brain region suggests that the mechanisms and cognitive strategies may be similar in both groups.

Differences were mainly bilateral mirroring the results from previous findings in MCI and controls (Maestu et al., 2008). The existence of patterns of bilateral activity while processing verbal stimuli could be interpreted in the framework of the HAROLD model (hemispheric asymmetry reduction in older adults) (Cabeza, 2002). This model proposes that older adults tend to recruit right hemisphere regions during verbal tasks to compensate for a lack of efficiency of the left hemisphere networks. The bilateral activation found in the present study could then reflect a compensatory mechanism in SMC and MCI patients.

Evidence for the existence of a compensatory mechanism in SMC patients has been recently reported in an elegant fMRI study (Rodda et al., 2009). This study found differences between SMC and controls in prefrontal regions, although no differences in ventral posterior regions were observed. Differences between studies could be due to the use of different neuroimaging techniques. While fMRI measures the level of blood flow and oxygenation MEG measures the magnetic fields induced by neural activity.

**Fig. 2.** Minimum-norm activity differences between patients with mild cognitive impairment and control volunteers. Average thresholded t-value across 100-ms windows. \( p < 0.05 \) corrected. Yellow circles indicate maxima and minima.
Furthermore brain activation was measured during the encoding stage in the fMRI study and during recognition in the MEG study, with information on rates of conversion to MCI, seems necessary. Future studies should determine whether the profiles of increased activity in the SMC group help predict the development of MCI.

To conclude, after excluding psychiatric conditions such as depression, SMC and MCI patients present similar biomagnetic records; however, both studies had in common that patients with psychiatric conditions had explicitly been excluded and that increases in activity were found for the SMC group.

While the neuropsychological tests failed to find evidence of cognitive impairment in the SMC participants, MEG recordings suggest that a similar mechanism, possibly of compensatory origin, may be in operation in both MCI and SMC groups. To test whether MEG can help detect very early cognitive impairment a longitudinal study, with information on rates of conversion to MCI, seems necessary. Future studies should determine whether the profiles of increased activity in the SMC group help predict the development of objective memory impairment. If possible, such studies should include SMC patients with and without depression and MCI patients with and without SMC.

To conclude, after excluding psychiatric conditions such as depression, SMC and MCI patients present similar biomagnetic profiles when compared to healthy elders without SMC (see also Maestu et al. (2008)). At the same time, no significant differences were found between the SMC and the MCI group. These findings suggest that similar physiological mechanisms may underlie both conditions indicating that SMC and MCI could be two stages on a cognitive continuum.

Disclosure

The authors report no conflicts of interest.

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