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A multicenter study of the early detection of synaptic dysfunction in Mild Cognitive Impairment using Magnetoencephalography-derived functional connectivity

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ABSTRACT

Synaptic disruption is an early pathological sign of the neurodegeneration of Dementia of the Alzheimer's type (DAT). The changes in network synchronization are evident in patients with Mild Cognitive Impairment (MCI) at the group level, but there are very few Magnetoencephalography (MEG) studies regarding discrimination at the individual level. In an international multicenter study, we used MEG and functional connectivity metrics to discriminate MCI from normal aging at the individual person level. A labeled sample of features (links) that distinguished MCI patients from controls in a training dataset was used to classify MCI subjects in two testing datasets from four other MEG centers. We identified a pattern of neuronal hypersynchronization in MCI, in which the features that best discriminated MCI were fronto-parietal and interhemispheric links. The hypersynchronization pattern found in the MCI patients was stable across the five different centers, and may be considered an early sign of synaptic disruption and a possible preclinical biomarker for MCI/DAT.

1. Introduction

Dementia of the Alzheimer's type (DAT) is the major cause of clinical dementia in the elderly (Qiu et al., 2009), and is characterized by the accumulation of the Beta amyloid protein, the phosphorylation of the Tau protein, and the loss of synapses. Amyloid deposition impairs normal inter-neuronal connectivity (Garcia-Marin et al., 2009), whereas Tau results in disruption of axonal microtubule organization (Taniguchi et al., 2001). The progressive loss of the number and efficiency of synapses disrupts inter- and intra-regional communication, leading to the idea that the DAT is a disconnection syndrome (Delbeuck et al., 2003;

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Selkoe, 2002; Morrison et al., 1991). As pathological changes associated with DAT start decades before the clinical symptoms appear, it is important to determine whether the pathophysiological changes, especially those at the level of the synapse, can be detected prior to the development of DAT.

Synaptic dysfunction and disruption of connectivity can be studied with Magnetoencephalography (MEG). MEG records the magnetic fields induced by intracellular postsynaptic activity (Hämäläinen, 1993), providing a direct measure of neuronal field potentials that can be used to assess the organization of brain functional architecture in DAT (Stam et al., 2009). The physiopathological characteristics of this disease could manifest differently at different stages of the disease. Thus, while advanced stages of DAT may be associated with functional disconnection, earlier stages may be apparent in terms of communication disruption (Buldu et al., 2011). Indeed, MEG studies of patients with Mild Cognitive Impairment (MCI), the intermediate clinical stage between normal cognition and dementia (Petersen, 2004), find that alterations in neuronal organization across the cortex seem to precede clinical dementia. MCI patients have increased synchronization over prefrontal and posterior regions (Bajo et al., 2010), and those who develop dementia within 2 years have higher synchronization than those who remain with MCI (Bajo et al., 2012; Lopez et al., 2014). Thus, hypersynchronization could be a hallmark of network disruption at early clinical stages of the disease.

However, some the existing MEG studies of MCI and DAT evaluated differences at the group level, but did not use blinded design or used only a small local sample of patients. For MEG to have the greatest utility in clinical practice, it must be able to detect changes in network dysfunction at the individual level, regardless of patient sample. The purpose of this study was to determine whether MEG could accurately classify individual MCI patients relative to cognitively normal elders. To accomplish this goal, we designed a blinded study that combined data from five different MEG centers, and used advanced data mining methods in order to extract features of MEG connectivity that best differentiated the patients from controls.

2. Methods

2.1. Study design

This study was executed in two training and two testing stages, using three separate datasets. Dataset 1 consisted of resting state MEG recordings from 78 MCI patients and 54 controls from a single laboratory in Madrid. Datasets 2 and 3 contained data from four other MEG centers (Dataset 2: 13 MCI patients and 15 controls, Dataset 3: 11 MCI patients and 13 controls) (see Table 1). In a first training stage, Dataset 1 was used to characterize the functional links that best discriminated MCI patients from controls, and the resulting model was tested with Datasets 2 and 3. This tested how a classifier trained on data from one site generalized to data from other sites. We then evaluated whether a classifier trained on multiple datasets was superior to one trained on a single dataset using Datasets 1 and 2, and tested on Dataset 3.

Table 1
Number of participants from each MEG center for each dataset.

	Dataset 1		Dataset 2		Dataset 3	
	NC	MCI	NC	MCI	NC	MCI
Madrid	54	78	–	–	—	—
Cambridge	—	—	3	3	9	6
Helsinki	–	–	6	4	1	2
Obu	–	–	3	3	3	3
Pittsburgh	–	–	3	3	0	0
Total	54	78	15	13	13	11

MCI: Mild Cognitive Impairment; NC: elderly control subjects.

2.2. Subjects

102 MCI patients (mean age 73.7 ± 5.1; 55% are female) and 82 age-matched controls (mean age 69.6 ± 4.6; 72% are female) participated in the study. They were recruited from five sites (Pittsburgh, Cambridge, Helsinki, Madrid, and Obu-Nagoya) as part of the activities of the MAGIC-AD group (Magnetoencephalography International Consortium for Alzheimer's Disease; see Zamrini et al., 2011).

Albert et al. (2011) proposed a terminology for classifying individuals with "MCI due to Alzheimer's Disease" with varying levels of certainty. When no biomarkers (e.g., amyloid PET or Tau values) are available, or in amyloid negative cases, the category of "MCI-core clinical criteria" can be still used. Thus, in this study we use this definition of MCI, as well the standard research criteria (Albert et al., 2011; Petersen, 2004), which require: 1) cognitive complaints corroborated by an informant; 2) objective cognitive impairment; 3) normal general cognitive function; 4) relatively preserved activities of daily living; and 5) not meeting the criteria for dementia. All participants in this group were classified with *amnestic* MCI. Participants were excluded if they had a history of any significant neurological disease, psychiatric disorders, or any significant systemic illness (e.g., advanced cancer or acute heart disease). The study was approved by the ethics committee at each MEG center, and all subjects gave written informed consent prior to participation.

2.3. Procedures

2.3.1. MEG acquisition

Each center used the same MEG protocol under similar conditions. Three to 5 minutes of eyes-closed resting state data were recorded while the participants were seated in a 306-channel Vectorview system (Elekta Oy, Helsinki, Finland) housed in a magnetically shielded room. MEG data were recorded at a sampling rate of 1000 Hz in Cambridge, Obu-Nagoya, Pittsburgh and Madrid, and at 1001.6 Hz in Helsinki (except for 4 subjects at 600–643 Hz). An online bandpass filter at 0.03–330 Hz was applied to all data at each site. The position of the head relative to the sensor array was monitored by four head position indicator coils attached to the scalp. For most subjects (108/132 in Dataset 1, 25/28 in Dataset 2, 24/24 in Dataset 3), head position was monitored continuously during the MEG recording, while for the remaining subjects only the initial head position was estimated. Electrooculograms were used to monitor eye movements (except for 4 subjects). A temporal signal space separation (tSSS) was applied to the MEG raw data in order to eliminate the contribution of non-brain sources to the MEG data, as proven useful in previous studies (Taulu and Simola, 2006; Nenonen et al., 2012; Gonzalez-Moreno et al., 2014). Maxfilter software (version 2.2, Elekta Neuromag) was used to perform the tSSS, along with a coordinate transformation into a common sensor space. We compared the level of magnetic noise in empty room recordings (i.e., without a subject present) and found that none of the centers had a noise level more than two standard deviations higher than the mean of the others. Thus recording sites were considered comparable.

2.3.2. MEG signal processing

MEG data preprocessing was performed with FieldTrip (Oostenveld et al., 2011), and was performed blind to diagnosis prior to the application of the classification algorithm. MEG recordings were filtered into classic frequency bands (Theta (4–8 Hz), Alpha (8–12 Hz), Beta (12–30 Hz), Gamma (30–45 Hz) and broadband (2–45 Hz)) with Finite Impulse Response (FIR) filters of order 1500. As delta activity (2–4 Hz) contains little time-related information in 2-s time windows (<8 oscillations), delta band was not employed for the present functional connectivity analysis. Then, the continuous resting state data were split into 2 s epochs. Ocular, muscular and jump artifacts were detected with