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Review

Alzheimer's disease: The state of the art in resting-state magnetoencephalography

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HIGHLIGHTS

- MEG activity in AD is slower, more regular, less complex and less well organized compared to healthy controls.
- Posterior and temporal areas are the most affected regions.
- MEG has currently not been used to its full potential.

ABSTRACT

Alzheimer's disease (AD) is accompanied by functional brain changes that can be detected in imaging studies, including electromagnetic activity recorded with magnetoencephalography (MEG). Here, we systematically review the studies that have examined resting-state MEG changes in AD and identify areas that lack scientific or clinical progress. Three levels of MEG analysis will be covered: (i) single-channel signal analysis, (ii) pairwise analyses over time series, which includes the study of interdependencies between two time series and (iii) global network analyses. We discuss the findings in the light of other functional modalities, such as electroencephalography (EEG) and functional magnetic resonance imaging (fMRI). Overall, single-channel MEG results show consistent changes in AD that are in line with EEG studies, but the full potential of the high spatial resolution of MEG and advanced functional connectivity and network analysis has yet to be fully exploited. Adding these features to the current knowledge will potentially aid in uncovering organizational patterns of brain function in AD and thereby aid the understanding of neuronal mechanisms leading to cognitive deficits.

Contents

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1. Introduction

Worldwide, approximately 35.6 million people are estimated to have dementia (World Health Organization, 2012). Dementia prevalence ranges between 1.6% and 6.4% in subjects over age 60 and increases disproportionally with advancing age (Ferri et al., 2005). Alzheimer's disease (AD) is the most common form of dementia and is known to be accompanied by abnormal neuronal activity that has been linked to amyloid beta depositions between neurons (Bero et al., 2011; Walker and Jucker, 2011). Although studies have indicated several potentially modifiable risk factors for AD (Norton et al., 2014), at this moment, no curative interventions are available. The development of therapeutic strategies is hindered by an incomplete understanding of both the relationship between neuronal activity and cognition, and of the underlying causes of AD.

In order to detect neuronal brain activity, functional imaging studies may come to our aid. Magnetoencephalography (MEG) has millisecond temporal-resolution such that information about neuronal activity can be captured with exquisite detail. MEG non-invasively records the small magnetic fields that are induced by electrical fields in the cerebral cortex.

Abnormal neuronal brain activity measured in AD has been reported extensively in recent years using a wide variety of analyses techniques, but mainly for electroencephalography (EEG; for reviews see Criado et al., 2006; Delbeuck et al., 2003; Hulbert and Adeli, 2013; Jeong, 2004; Micanovic and Pal, 2014). On a single-channel level (i), the frequency spectrum can be evaluated as well as the nonlinear components of a signal (Stam, 2005). The latter method aims to estimate future dynamics of specific time series with respect to the previous dynamics (autocorrelation). These dynamical analyses can also be applied to pairwise analyses (ii) over time series in which previous dynamics of two time series try to predict the future dynamics of time series of interest. Furthermore, pairwise channel analyses have been used to estimate functional connection between distant brain areas (Friston, 2011; Pereda et al., 2005). This functional connectivity, or statistical interdependency of time series is assumed to reflect functional interactions between the underlying brain areas, regardless of direct structural connections. This approach allows the appreciation of the overall organization, rather than strength, of connections, which is likely to be optimized in healthy subjects and impaired in AD (Stam et al., 2009; Tijms et al., 2013). On the other hand, effective connectivity reflects the direction of the connectivity, i.e. the influence of one region over the other (Friston, 2011). Functional and effective connectivity are indicative of macroscopic neuronal communication and may be especially relevant in dementia, where disturbances in this communication have been related to cognitive deficits (Delbeuck et al., 2003; Knyazeva et al., 2013). Imaging studies on coordinated brain activity have contributed to the understanding of the brain's functional organization, as a representation of the brain as a global network (iii), by disclosing several generic properties: healthy brain networks appears integrated in a hierarchical, modular fashion (Stam and van Straaten, 2012), and has been related to cognitive performance and intelligence (Douw et al., 2011, 2014; van den Heuvel et al., 2009). Individuals suffering from AD show alterations in brain activity, functional connectivity, and functional network topology, but the nature of these changes, and the relation with cognitive decline, is not yet fully understood.

Previously, resting-state network studies have shown that the functional changes in AD are not randomly distributed over the brain, but are focused in certain brain areas. In resting-state studies of healthy controls, a combination of brain areas referred to as the default mode network (DMN) show coordinated activity (Greicius et al., 2004; Rosazza and Minati, 2011). Several regions in the parietal and temporal lobes, including the precuneus / posterior cingulate gyrus and hippocampus, are highly active DMN components, that play a central role (i.e. they form hubs) in the functional and structural brain networks (Buckner et al., 2008). However, although several DMN components are regarded as hubs, not all hubs in brain networks are part of the DMN. It has been shown that regions of the DMN are preferentially vulnerable to neurodegeneration, not only in AD but also in a symptomatic pre-stage of AD (Hsiao et al., 2013). In AD, the posterior part of the DMN, including the parasagittal parietal and posterior temporal areas, is particularly affected as shown in fMRI, EEG and MEG (Buckner et al., 2009; Engels et al., 2015; de Haan et al., 2012a,b; Li et al., 2015). It has been suggested that preferential damage to hub-like brain regions in AD is related to high baseline local neuronal activity. A computational model study showed indeed that highly connected regions have a high neuronal firing rate and spectral power (de Haan et al., 2012c). Furthermore, activity-dependent degeneration was able to reproduce the AD-like changes that have been observed experimentally, such as oscillatory slowing, loss of spectral-power and long-range functional connections, as well as disrupted functional network topology, including hub vulnerability (de Haan et al., 2012c).

Currently, there is no recent review of MEG studies investigating preferential hub damage in AD. In addition, while electroencephalography (EEG) studies in AD have been reviewed extensively (e.g. Adeli et al., 2005; Bhat et al., 2015; Dauwels et al., 2010; Ferrazzoli et al., 2013; Jeong, 2004; Lim et al., 2014; Micanovic and Pal, 2014; van Straaten et al., 2014), such reviews of MEG findings are less prevalent (Stam, 2010, 2014). We therefore set out to review the current literature to identify differences as well as consistencies in results regarding eyes-closed task-free MEG in AD. In addition, we determined whether MEG studies provide more detailed anatomical information about abnormalities than EEG, and identify gaps in our knowledge as well as new questions for future research.

2. Methods

We performed a PubMed search with combinations of the following key words: magnetoencephalography (MEG), Alzheimer's