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Magnetoencephalographic evaluation of resting-state functional connectivity in Alzheimer's disease

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Statistical interdependencies between magnetoencephalographic signals recorded over different brain regions may reflect the functional connectivity of the resting-state networks. We investigated topographic characteristics of disturbed resting-state networks in Alzheimer's disease patients in different frequency bands. Whole-head 151-channel MEG was recorded in 18 Alzheimer patients (mean age 72.1 years, SD 5.6; 11 males) and 18 healthy controls (mean age 69.1 years, SD 6.8; 7 males) during a no-task eyes-closed resting state. Pair-wise interdependencies of MEG signals were computed in six frequency bands (delta, theta, alpha1, alpha2, beta and gamma) with the synchronization likelihood (a nonlinear measure) and coherence and grouped into long distance (intra- and interhemispheric) and short distance interactions. In the alpha1 and beta band, Alzheimer patients showed a loss of long distance intrahemispheric interactions, with a focus on left fronto-temporal/parietal connections. Functional connectivity was increased in Alzheimer patients locally in the theta band (centro-parietal regions) and the beta and gamma band (occipito-parietal regions). In the Alzheimer group, positive correlations were found between alpha1, alpha2 and beta band synchronization likelihood and MMSE score. Resting-state functional connectivity in Alzheimer's disease is characterized by specific changes of long and short distance interactions in the theta, alpha1, beta and gamma bands. These changes may reflect loss of anatomical connections and/or reduced central cholinergic activity and could underlie part of the cognitive impairment.

Keywords: Alzheimer's disease; Resting state; Functional connectivity; MEG; Synchronization likelihood; Crosscorrelation; Coherence; Cognition

Introduction

The neurophysiological mechanisms that underlie cognitive and behavioral dysfunction in Alzheimer's disease (AD) are still incompletely understood. Despite an enormous increase in knowledge about the cellular, molecular, vascular (chronical cerebral hypoperfusion) and genetic processes involved in AD pathology, the relationship between these fundamental changes and abnormal functioning of large scale brain networks remains unclear.

One approach to this problem has concentrated on the idea that AD pathology at the cellular and molecular level could give rise to impaired activation of specific brain regions or a slowing down of local electrophysiological oscillatory activity. Evidence for such local abnormalities has been found with fMRI studies showing impaired activation, in particular, of the hippocampus and related areas during memory tasks (Rombouts et al., 2000). Neurophysiological techniques such as EEG and more recently MEG have also been used to identify local physiological abnormalities (for a review, see Jeong, 2004). EEG studies have demonstrated a slowing of the dominant rhythms, in particular, over the posterior temporal parietal and occipital brain areas (Boerman et al., 1994; Jeong, 2004; Jonkman, 1997). This EEG slowing has been correlated with brain atrophy, APOE genotype and low central cholinergic activity (Lehtovirta et al., 1996; Riekkinen et al., 1991). MEG studies have confirmed the notion of a slowing of brain rhythms and have also suggested an anterior displacement of the sources of these rhythms (Berendse et al., 2000; Fernandez et al., 2002, 2003, 2006; Maestu et al., 2001, 2003, 2004, 2005; Osipova et al., 2005). However, a limitation of these approaches is that it is unclear how these local abnormalities influence the functioning of the brain as an integrated system.

A promising alternative approach focuses on connections rather than on local dysfunction. A central problem in cognitive neuroscience is the question how different, widely distributed

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and specialized brain areas integrate their activity. It is widely believed that such large scale functional integration is crucial for higher cognitive and behavioral functioning (Fuster, 2003; Mesulam, 1990, 1998; Tononi et al., 1998). One candidate mechanism for large scale functional integration is the phenomenon of synchronization or temporal correlations between neural activity in different brain regions (Le van Quyen, 2003; Varela et al., 2001). Synchronization of brain regions can be studied by measuring statistical interdependencies (functional connectivity) between physiological signals such as fMRI BOLD, EEG or MEG from different brain regions either during a resting state or during a task (Lee et al., 2003; Fingelkurts et al., 2005; Pereda et al., 2005; Stam, 2005). Studies of functional connectivity have revealed the existence of synchronized neural networks in different frequency bands and involving different brain regions. For instance, working memory is associated with long distance interactions in the theta band, while gamma synchronization may be related to perception and consciousness (Rodriguez et al., 1999; Sarnthein et al., 1998; Stam et al., 2002a; Micheloyannis et al., 2005). Large scale low frequency synchronization has been associated with a context of cognition, while smaller scale high frequency synchronization might be related to content (Palva et al., 2005).

This raises the question whether AD is perhaps better characterized by abnormalities at the network level in addition to, or instead of, the well-known local disturbances. Disturbed functional connectivity would support a 'disconnection hypothesis' of cognitive dysfunction in AD (Delbeuck et al., 2003). Several EEG studies have demonstrated a lower coherence, a linear measure of functional connectivity, of EEG, especially in the alpha band, in AD (Adler et al., 2003; Babiloni et al., 2004a; Besthorn et al., 1994; Dunkin et al., 1994; Hogan et al., 2003; Jelic et al., 1996; Jiang, 2005; Koenig et al., 2005; Knott et al., 2000; Leuchter et al., 1992; Locatelli et al., 1998; Pogarell et al., 2005; Stevens et al., 2001). Changes in coherence outside the alpha band have been reported less frequently, and controversy exists about the question whether delta and theta band coherence are decreased or increased in AD.

Use of nonlinear measures has also suggested a loss of functional connectivity in AD, especially in the alpha and beta bands (Babiloni et al., 2004a,b; Jeong et al., 2001; Pijnenburg et al., 2004; Stam et al., 2003a). MEG may be more suitable than EEG to assess functional connectivity since MEG does not require the use of a reference and is more sensitive to nonlinear correlations (Stam et al., 2003b). In a pilot study, Berendse et al. showed a lower coherence in all frequency bands in AD patients (Berendse et al., 2000). More recently, we used the synchronization likelihood, a measure of generalized synchronization, to study functional connectivity in a larger group of AD subjects and controls (Stam and van Dijk, 2002; Stam et al., 2002b). This study revealed a lower level of synchronization in the upper alpha band, the beta and the gamma band in AD (Stam et al., 2002b). However, lower levels of functional connectivity per se may not yet explain why the large scale brain networks are functioning abnormally. Recently, we found that in AD abnormal topographic organization of large scale brain networks was present, with loss of so called 'small-world' features which correlated with MMSE scores (Stam et al., 2006). This points to the possibility that in AD a specific loss of certain long or short distance connections occurs, involving brain regions at risk in AD.

The present study was undertaken to study in more detail resting-state functional connectivity changes in AD. In particular, we addressed the question whether AD might be associated with a specific loss of either long distance or short distance interactions in particular regions and frequency bands. To this end, MEG was recorded during an eyes-closed no-task state in 18 AD patients and 18 healthy controls. The synchronization likelihood and coherence were computed between all pairs of sensors for signal filtered in delta, theta, alpha1, alpha2, beta and gamma bands. SL and coherence values were averaged for long distance (intra- and interhemispheric) and short distance local sensor pairs.

Methods

Subjects

The study involved 18 patients (mean age 72.1 years, SD 5.6; 11 males; mean MMSE 19.2, range: 13–25) with a diagnosis of probable AD according to the NINCDS-ADRDA criteria (McKhann et al., 1984) and 18 healthy control subjects (mean age 69.1 years, SD 6.8; 7 males; mean MMSE 29, range: 27–30), mostly spouses of the patients. Patients and control subjects were recruited from the Alzheimer Center of the VU University Medical Center. Subjects were assessed according to a clinical protocol, which involved history taking, physical and neurological examination, blood tests, MMSE (Folstein et al., 1975) neuropsychological work up (administration of a battery of neuropsychological tests), MRI of the brain according to a standard protocol and routine EEG. The final diagnosis was based upon a consensus meeting where all the available clinical data and the results of the ancillary investigations were considered. The study was approved by the Local Research Ethics Committee, and all patients or their caregivers had given written informed consent.

MEG recording

Magnetic fields were recorded while subjects were seated inside a magnetically shielded room (Vacuumschmelze GmbH, Hanau, Germany) using a 151-channel whole-head MEG system (CTF Systems Inc., Port Coquitlam, BC, Canada). Average distance between sensors in this system is 3.1 cm. A third-order software gradient (Vrba et al., 1999) was used with a recording pass band of 0.25 to 125 Hz. Sample frequency was 625 Hz. Fields were measured during a no-task eyes-closed condition. At the beginning and at the end of each recording, the head position relative to the coordinate system of the helmet was recorded by leading small alternating currents through three head position coils attached to the left and right pre-auricular points and the nasion on the subject's head. Head position changes during the recording up to approximately 1.5 cm were accepted. During the MEG recording, patients were instructed to close their eyes to reduce artefact signals due to eye movements.

For further off-line processing, the recordings were converted to ASCII files and down-sampled to 312.5 Hz. For each subject, three artefact-free epochs of 4096 samples (13,083 s) were selected by two of the investigators (BFJ and IM). Visual inspection and selection of epochs were done with the DIGEEGXP software (CS).

Nonlinear data analysis

Nonlinear correlations between all pair-wise combinations of MEG channels were computed with the synchronization

likelihood (Stam and van Dijk, 2002). Mathematical details can be found in Appendix A; here, we give a brief description. The synchronization likelihood (SL) is a general measure of the correlation or synchronization between two time series which is sensitive to linear as well as nonlinear interdependencies. The SL fluctuates around P_{ref} (a small positive number) in case of independent time series and reaches the value of 1 in case of maximally synchronous signals. P_{ref} is a parameter which has to be chosen; in the present study, P_{ref} was set at 0.01. The basic principle of the SL is to divide each time series into a series of 'patterns' (roughly, brief time intervals containing a few cycles of the dominant frequency) and to search for a recurrence of these patterns. The SL then is the chance that pattern recurrences in time series X coincide with pattern recurrences in time series Y; P_{ref} is the small but non-zero likelihood of coincident pattern recurrence in the case of independent time series. The end result of computing the SL for all pair-wise combinations of channels is an $N \times N$ matrix with N equal to 149 (sensor 150 and 151 were not used), where each entry $N_{i,j}$ contains the value of the SL for the channels i and j.

SL was computed for the following frequency bands: delta (0.5–4 Hz), theta (4–8 Hz), alpha1 (8–10 Hz), alpha2 (10–13 Hz), beta (13–30 Hz) and gamma (30–45 Hz). Digital, zero-phase lag filtering was done off-line. Results for the three epochs were averaged. Further averaging was done to obtain long distance intra- and interhemispheric and short distance local measures. For this, MEG channels were grouped into (left and right) central, frontal, occipital, parietal and temporal regions (based upon the naming of the CTF sensors). Long distances (8 intrahemispheric: fronto-temporal, fronto-parietal, parieto-occipital, occipito-temporal; 5 interhemispheric: central, frontal, occipital, parietal and temporal) involved correlations between two different regions (within one hemisphere and homologue regions of two hemispheres), and short distances involved correlations within one region. Midline sensors were not used. The procedure is illustrated in Fig. 1.

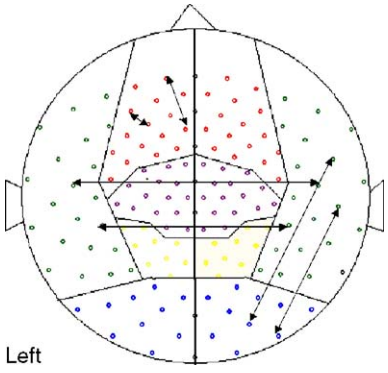

Fig. 1. Illustration of the allocation of sensor pairs to short and long distances. The figure shows the sensor positions of the CTF MEG system projected onto a two-dimensional surface. Sensors are grouped into frontal (red), central (purple), parietal (yellow), occipital (blue) and temporal (green) regions for both hemispheres. The short distance SL was computed as the average SL between all sensor pairs within one region (two such pairs are shown for the left frontal region). Long distance SL was computed from sensor pairs where one sensor was in one region, and the other sensor was in another region. This is illustrated for right occipito-temporal long distance SL and for temporal interhemispheric long distance SL.

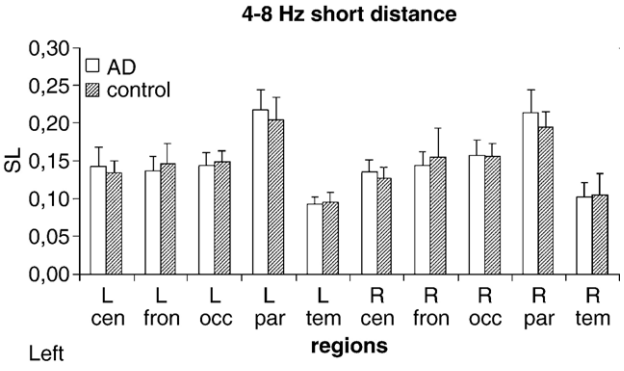

Fig. 2. Mean theta band SL (error bars indicate standard deviation) of Alzheimer patients and healthy controls for ten local regions (L = left; R = right hemisphere. cen = central; fron = frontal; occ = occipital; par = parietal; tem = temporal). For each region, the mean SL values obtained for all possible pairs of sensors within that region were averaged. SL was higher in Alzheimer patients at left and right central and parietal regions; in the other regions, SL in the patients was lower than or equal to that of the control subjects.

Linear analysis

Linear correlations between all pair-wise combinations of MEG channels were computed with coherence analysis (Nunez et al., 1997; Nolte et al., 2004).The complex coherency between two time series can be defined as the cross spectrum divided by the product of the two power spectra. As described by Nolte et al. (2004), its mean overall frequencies can alternatively be computed via the mean over time of the corresponding analytical signals like:

$$c = \frac{\langle A_1 A_2 e^{i\Delta\phi} \rangle}{\sqrt{\langle A_1^2 \rangle \langle A_2^2 \rangle}} \quad (1)$$

Here, A_1 and A_2 are the amplitudes of the two time series, and $\Delta\phi$ is the instantaneous phase difference between (the Hilbert transforms of) the two time series. The absolute value of coherency is coherence bounded between 0 and 1. Coherence was computed all for pairs of channels, for the six frequency bands described above. Results were averaged for long distance intra- and interhemispheric and short distance channel pairs as described for the synchronization likelihood. For the beta band, we also computed the crosscorrelation (correlation coefficient between the two time series) to check whether any significant effects detected by this basic measure would also be picked up by the coherence and SL analysis.

Statistical analysis

Statistical analysis was done with SPSS for Windows (version 10.0.7). For each frequency band, three separate repeated-measures ANOVAs were done, using Greenhouse–Geisser corrected degrees of freedom to correct for lack of sphericity. In some cases (when the ANOVA showed significant main effects or interactions), t test was used for detailed analysis. For the long distance intrahemispheric data, the repeated-measures factor had 8 levels (left and right fronto-temporal, fronto-parietal, parieto-occipital, occipito-temporal); for the long distance data, the repeated-measures factor had 5 levels (central, frontal, occipital, parietal and temporal) and for the short distance data the

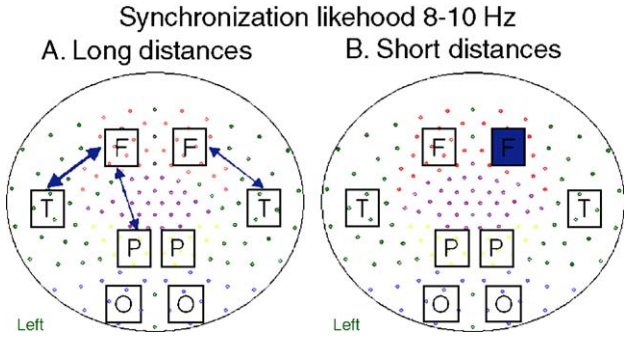

Fig. 3. Schematic illustration of SL (SL) results for the alpha1 band. A. Long distances. Decrease of bilateral fronto-temporal and left fronto-parietal SL in Alzheimer patients. B. Short distances. Local decrease of SL in right frontal region. Lines correspond to significant changes of average SL between two regions and squares to significant changes of local SL (thin line/light square: $P < 0.05$; thick line/dark square: $P < 0.01$; blue: Alzheimer lower than controls; red: Alzheimer higher than controls; significance is based upon two-tailed t tests and intended for illustration; formal testing was based upon a repeated-measures ANOVA).

repeated-measures factor had 10 levels (left and right central, frontal, occipital, parietal and temporal). The group factor had two levels (Alzheimer/control). Age was not used as a covariate since the age difference between the groups was not significant. A significance level of $P < 0.05$ was used.

Results

Nonlinear analysis

The delta band showed no significant effects involving the factor Group. In the theta band, a significant Group × Region interaction ($F[9,306] = 2.604$; $P = 0.029$) was found for short distances. This interaction effect is illustrated in Fig. 2. Inspection of Fig. 2 shows that the SL was higher in AD patients compared to controls in the right and left parietal and to a lesser extent central regions. This difference was significant for the right parietal region

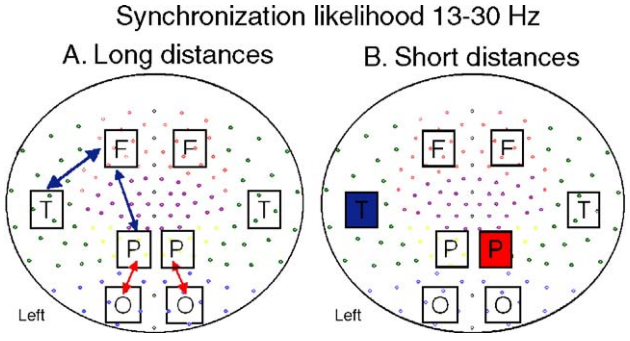

Fig. 4. Schematic illustration of SL (SL) results for the beta band. A. Long distances. Decrease of left fronto-temporal and fronto-parietal SL and increase in bilateral occipito-parietal SL in Alzheimer patients. B. Short distances. Local increase of SL in right parietal region and local decrease of SL in left temporal region. Lines correspond to significant changes of average SL between two regions and squares to significant changes of local SL (thin line/light square: $P < 0.05$; thick line/dark square: $P < 0.01$; blue: Alzheimer lower than controls; red: Alzheimer higher than controls; significance is based upon two-tailed t tests and intended for illustration; formal testing was based upon a repeated-measures ANOVA).

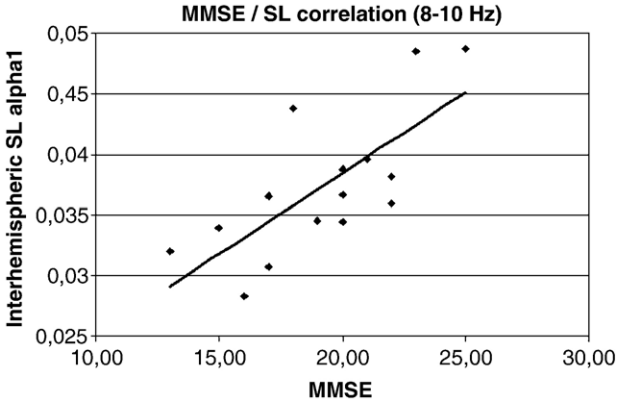

Fig. 5. Correlation between MMSE (15 Alzheimer patients for whom a score was available) score and averaged interhemispheric SL in the alpha1 band. $R = 0.727$; $P = 0.002$.

(two-sided t test, $P = 0.037$) In the other regions, SL was slightly lower in the AD group or comparable between the two groups. The interaction thus reflects a selective increase of SL in the central parietal areas in the AD patients.

In the alpha1 band, a significant main effect of Group was found ($F[1,34] = 5.745$; $P = 0.022$) for long distance intrahemispheric connections. This Group effect is illustrated schematically in Fig. 3. SL was lower in the AD group compared to the control group; the most significant changes involved the left fronto-temporal (t test: $P = 0.009$), left fronto-parietal (t test: $P = 0.012$) an the right fronto-temporal (t test: $P = 0.015$) connections.

The alpha2 band showed no significant effects involving the factor Group. In the beta band, two significant interactions were present: the first involved a significant Group × Region interaction ($F[7,238] = 4.042$; $P = 0.023$) for long distance intrahemispheric connections, and the second one a significant Group × Region interaction ($F[9,306] = 3.610$; $P = 0.006$) for short distance connections. These interaction effects are illustrated schematically in Fig. 4.

For all the frequency bands, correlations between SL measures and MMSE scores were computed. The correlations were computed for the AD subjects only. For the delta, theta and gamma bands, no significant correlations were found. For the alpha1 band, significant positive correlations were found between

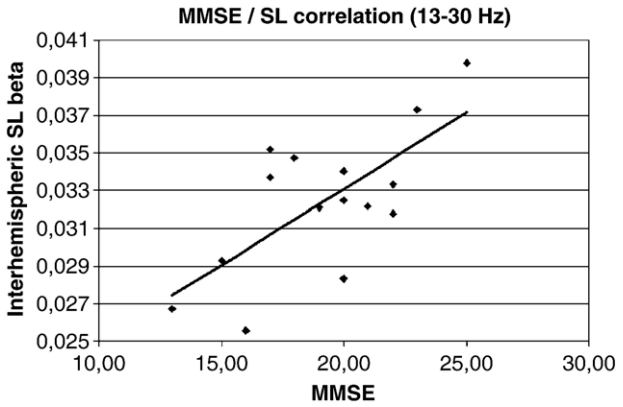

Fig. 6. Correlation between MMSE (15 Alzheimer patients for whom a score was available) score and averaged interhemispheric SL in the beta band. $R = 0.688$; $P = 0.005$.

the MMSE score and average interhemispheric SL ($R = 0.727$; $P = 0.002$), interhemispheric temporal SL ($R = 0.632$; $P = 0.011$), left frontal ($R = 0.673$; $P = 0.006$) and right frontal SL ($R = 0.551$; $P = 0.033$). The correlation between MMSE and average interhemispheric SL is shown in Fig. 5.

For the alpha2 band, significant positive correlations between SL and MMSE were found for interhemispheric connections ($R = 0.690$; $P = 0.005$), temporal interhemispheric connections ($R = 0.578$; $P = 0.024$), left frontal local connections ($R = 0.532$; $P = 0.041$) and left temporal local connections ($R = 0.526$; $P = 0.044$). In the beta band, significant positive correlations between SL and MMSE were found for right temporo-occipital connections ($R = 0.599$; $P = 0.018$), average interhemispheric SL ($R = 0.688$; $P = 0.005$) and interhemispheric temporal SL ($R = 0.619$; $P = 0.014$). The correlation between MMSE and average interhemispheric SL is shown in Fig. 6.

Linear analysis

Coherence showed no significant effects of Group or Group × Region interactions for the delta, theta and alpha1 bands. In the alpha2 band, there was a significant Group × Region interaction for short distances ($F[9,306] = 2.372$; $P = 0.033$). Post hoc t tests only showed a higher coherence in AD patients at the right parietal region (t test: $P = 0.026$). In the beta band, there was a significant Group × Region interaction for long intrahemispheric distances ($F[7,238] = 4.044$; $P = 0.012$) and for short distances ($F[9,306] = 4.700$; $P = 0.001$). These interactions are illustrated in Fig. 7. AD patients had a lower left fronto-temporal coherence (t test: $P = 0.010$) and a higher left (t test: $P = 0.038$) and right (t test: $P = 0.004$) parietal coherence. Short distance coherence was lower in the AD group in the left temporal region (t test: $P = 0.044$) and higher in left (t test: $P = 0.016$) and right (t test: $P = 0.001$) parietal regions. In the gamma band, there was a significant main effect of Group for long distances ($F[1,34] = 4.755$; $P = 0.036$). AD patients had higher left (t test, $P = 0.023$) and right (t test, $P = 0.003$) parieto-occipital coherence.

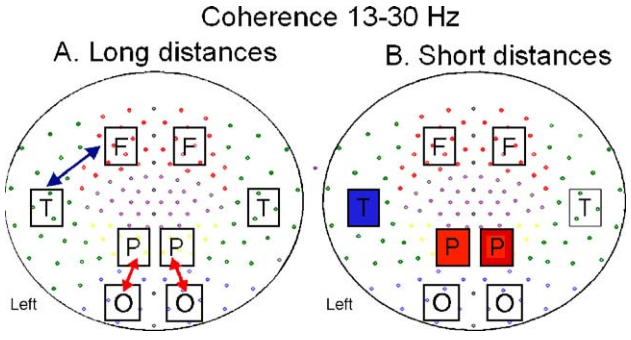

Fig. 7. Schematic illustration of coherence results for the beta band. A. Long distances. Decrease of left fronto-temporal coherence and increase in bilateral occipito-parietal coherence in Alzheimer patients. B. Short distances. Local increase of coherence in right and left parietal regions and local decrease of SL in left temporal region. Lines correspond to significant changes of average coherence between two regions and squares to significant changes of local coherence (thin line/light square: $P < 0.05$; thick line/dark square: $P < 0.01$; blue: Alzheimer lower than controls; red: Alzheimer higher than controls; significance is based upon two-tailed t tests and intended for illustration; formal testing was based upon a repeated-measures ANOVA).

For the beta band, results were checked with a crosscorrelation analysis. For long distance intrahemispheric crosscorrelations, there was a significant Group × Region interaction ($F[7,238] = 4.013$; $P = 0.005$). t tests showed a lower correlation in the AD group for left fronto-temporal connections (t test: $P = 0.006$) and higher correlations in the AD group for left (t test: $P = 0.010$) and right (t test: $P = 0.023$) parieto-occipital connections. For long distance, interhemispheric correlations no significant effects were found. For short distances, a significant Group × Region interaction was found ($F[9,306] = 4.009$; $P = 0.003$). The correlation was lower in the AD group at left temporal (t test: $P = 0.017$) and right frontal (t test: $P = 0.038$) locations; it was higher in the AD group at left (t test: $P = 0.012$) and right (t test: $P = 0.001$) parietal regions.

Discussion

This study demonstrated a specific pattern of changes in resting-state functional connectivity in AD patients. SL was increased in the theta band over the central and parietal areas and in the beta band over the parietal and occipital areas. Coherence showed a similar pattern of parieto-occipital increase in AD in alpha2, beta and gamma bands. In contrast, SL was decreased in the alpha1 band for long distance intrahemispheric sensor pairs, and both SL and coherence (and crosscorrelation) were decreased in the beta band for long distance frontal temporal/parietal and short distance left temporal sensor pairs. Lower SL, especially for temporal interhemispheric connections correlated with disease severity as expressed by a lower MMSE score.

In studies of this kind, it is always important to consider the question whether correlations between signals recorded at different sensors can be interpreted in terms of physiological interactions between different brain regions. In the case of EEG, an active reference electrode can cause spurious correlations between signals recorded at different electrodes (Guevara et al., 2005; Nunez et al., 1997). MEG does not require the use of a reference electrode and thus may be more suitable for estimating functional connectivity than EEG (Guevara et al., 2005). However, even with MEG correlations between signals from nearby sensors could be due to common sources rather than true interactions. Furthermore, the location of the sources giving rise to the signal recorded at the sensors is generally not known. This is the well-known problem of volume conduction that may give rise to spurious correlations in sensor space.

One possible solution is to estimate correlations between signals from reconstructed sources ('source space') rather than the actually recorded signal ('signal space') (David et al., 2002; Gross et al., 2001; Hadjipapas et al., 2005). However, no unique way exists to reconstruct the sources, and the source reconstruction algorithm used could influence the interdependencies between the sources (Hadjipapas et al., 2005). A possible alternative is the use of the imaginary component of the coherency, which is not sensitive to a linear mixing of independent sources (Nolte et al., 2004). However, even this approach may not always be effective (Wheaton et al., 2005). In the present study, we adopted a pragmatic approach, restricting the analysis to signal space, and grouping the sensor pairs in long and short distances. While SL and coherence estimated in this way will be influenced by volume conduction, it is less likely that volume conduction can explain group differences in SL between AD patients and controls.

Furthermore, several of our main results involve changes in long distance interactions which are less likely to be due to volume conduction. Note that changes observed in regions of the signal space cannot be interpreted as reflecting physiological changes in the brain regions underlying the sensors. Even so, we should stress that MEG is especially sensitive to superficial cortical sources. The changes over parietal regions we describe are supported by MRI findings with voxel-based morphometry (Karas et al., 2004).

Theoretically, estimates of statistical interdependencies between different channels could also be influenced by differences in signal power. Assuming a constant level of measurement/background noise, signals with lower power could be expected to have a lower signal-to-noise ration. A lower SNR ration might produce biased lower values of functional connectivity. However, we consider it unlikely that the main results of the present study can be explained in this way. The absolute signal power in the beta band in the AD group was either comparable to or lower than the power in the control group (Fig. 8). All three measures (SL, coherence and crosscorrelation) showed an increase of parieto-occipital connectivity in the AD group, while the power in the AD group was significantly lower in the parietal and occipital regions. Furthermore, the significant loss of connectivity in left fronto-temporal regions in the AD group was not associated with significant power changes at all. Thus, the assessment of functional connectivity provides information that is independent from signal power and is more likely related to functional interactions between brain regions.

Another methodological consideration concerns the use of drugs that influence the cholinergic system. In theory, such drugs could influence the EEG and the MEG, most likely by reverting the slowing and loss of connectivity due to the AD pathology (Adler and Brassen, 2001; Osipova et al., 2003). In our study, 6 of the 18 patients used cholinesterase inhibitors. To determine the possible influence of drug use on our results, we compared the SL (averaged over all possible pairs of sensors) in the theta, alpha1 and beta band between AD patients who did and who did not use cholinesterase inhibitors. No significant differences were found which suggests that our results are unlikely to be strongly influenced by medication effects.

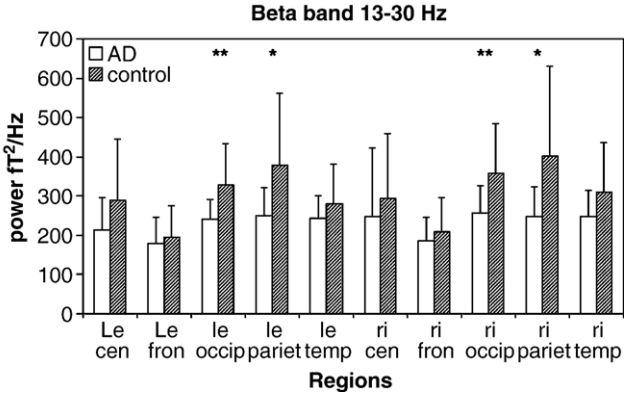

Fig. 8. Mean beta band absolute power (error bars indicate standard deviation) of Alzheimer patients and healthy controls for ten local regions (L = left; *R* = right hemisphere. cen = central; fron = frontal; occ = occipital; par = parietal; tem = temporal). For each region, the mean power values obtained for all sensors within that region were averaged. Power was significantly lower in Alzheimer patients at left and right parietal and occipital regions. **t* test: $P < 0.05$ ***t* test: $P < 0.01$.

Our study was conducted during an eyes-closed no-task condition. One might ask whether such a 'resting state' is the most effective condition for demonstrating abnormalities of functional connectivity in AD. For instance, a recent EEG study using spectral analysis and cognitive tasks has suggested that task-induced EEG changes might increase the discrimination between controls and MCI subjects (van der Hiele et al., 2006). However, a number of recent fMRI studies have shown that the resting state is a far more stable and active condition than has often been assumed (Gusnard and Raichle, 2001). The resting state is characterized by the activation of a 'default' network, which consists of frontal, posterior cingulate, parietal and medial temporal areas (Laufs et al., 2003). Abnormalities of this resting-state network have been demonstrated in AD (Lustig et al., 2003). Although the use of specific tasks, aimed at activating brain areas assumed to be involved in AD, might be expected to be more sensitive in demonstrating abnormalities, this is often not the case. One reason may be that the pathology may be associated with abnormally high as well as abnormally low task-related activation, which seriously complicates interpretation of the results (Osipova et al., 2005; Pijnenburg et al., 2004). Furthermore, the present study confirms that a simple resting-state condition is sufficient to demonstrate widespread changes in functional connectivity in AD. The relevance of resting-state SL for cognition is further supported by the fact that alpha1 and beta band SL, especially involving interhemispheric temporal connections, were positively correlated to MMSE scores.

The pattern of functional connectivity changes in the present study shows similarities as well as differences with previous EEG and MEG work. A lower level of synchronization in alpha band and beta band has been reported by most earlier EEG and MEG studies (Adler et al., 2003; Babiloni et al., 2004a; Besthorn et al., 1994; Dunkin et al., 1994; Hogan et al., 2003; Jelic et al., 1996; Jiang, 2005; Koenig et al., 2005; Knott et al., 2000; Leuchter et al., 1992; Locatelli et al., 1998; Pogarell et al., 2005; Stevens et al., 2001). In contrast to our previous MEG study (Stam et al., 2002b), we found a loss of lower instead of upper alpha band synchronization. Two factors may be involved in the differences between the present and previous MEG study: (i) the different way in which the embedding parameters L and M were chosen; (ii) the different choice of frequency bands.

In the 2002 study, the choice of L and M for the computation of the SL was still fairly arbitrary. Recently, it has been shown that an incorrect choice of L and M can result in unexpected frequency content of the patterns considered by the SL algorithm and that a proper choice of L and M should take into account the low and high frequency filters settings (Montez et al., submitted for publication). In the present study, we used a different approach to the choice of L and M based explicitly on the frequency content of the data (Montez et al., submitted for publication). There was also a different definition of the two alpha bands in the two studies: in the previous 2002 study, alpha1 was defined as 6–10 Hz and alpha2 as 10–14. Hz. Failure to find an effect in the lower alpha band in the 2002 study could be due to the fact that this band incorporated part of the theta band, where, as shown in the present study, changes are in the opposite direction. The significant effect in the upper alpha band in the 2002 study might be caused by incorporating part of the beta band, which showed a significant effect in both studies, as well as in EEG studies of SL (Stam et al., 2003a; Pijnenburg et al., 2004). In a similar way, the significant gamma band effects of the 2002 study partly overlap the beta band

results of the present study. With SL, we could not demonstrate significant effects in a higher gamma band of 30–45 Hz. In an EEG study, Babiloni et al. demonstrated a lower SL in a wide range of frequencies in AD patients (Babiloni et al., 2004b). This could be due to the much larger group size of this study, although the larger age difference between controls and patients might also have influenced the results. In the present study, no significant age effects were present between patients and controls.

The principal aim of the present study was to determine the relative contribution of long distance and short distance interactions in different frequency bands to impaired functional connectivity in AD. Short and long distance interactions might underlie local specialization and global integration of brain dynamics, which have to be balanced to ensure optimal information processing (Tononi et al., 1998; Van Cappellen van Walsum et al., 2003). We used the SL as well as the more commonly used coherence to study the contribution of short and long distance interactions. We expected SL to be sensitive to both nonlinear as well as linear aspects of a correlation, i.e. detects interdependencies between complex patterns that can be different in each channel and would not be detected by classical measures. In the present study, SL showed group differences in the theta and alpha1 that were not detected by coherence. In the beta band, both SL and coherence (as well as the crosscorrelation analysis) detected a similar pattern of fronto-temporal decrease and parieto-occipital increase in AD. In the alpha2 and gamma band, coherence revealed changes that were not picked up by SL. We have previously shown that SL may be more sensitive than coherence in detecting subtle differences between controls and AD patients (Stam et al., 2002b). Furthermore, SL can detect weak nonlinear coupling which has been demonstrated in MEG recordings (Stam et al., 2003b). The results of the present study show a more complex picture which might be due to the fact that we have now taken into account the spatial details of connectivity: in some cases, linear and nonlinear measures perform equally well, in other cases, one of the two approached may reveal information not picked up by the other approach.

Lower SL in the alpha1 band was restricted to long distance, intrahemispheric fronto-temporal and fronto-parietal interactions. This might reflect loss of long distance association fibers connecting frontal, temporal, parietal and occipital areas. The beta band also showed a loss of long distance intrahemispheric linear and nonlinear connectivity, involving especially left frontal, temporal and parietal connections. Although interhemispheric correlations were not significantly lower in AD subjects, the SL did show a strong correlation with lower MMSE scores. Of interest, lower interhemispheric coherence in AD has been shown to be correlated with atrophy of the corpus callosum (Pogarell et al., 2005). This further supports the concept that lower long distance synchronization might reflect loss of anatomical connections. Two studies suggest that the relationship between long distance anatomical connections and functional connectivity could be partly genetically determined. In a large study in twins, it was shown that alpha band SL was strongly inherited (Posthuma et al., 2005). Lower EEG coherence in AD has been associated with the e4 allele of the APOE genotype (Jelic et al., 1997).

Short distance linear and nonlinear interactions in the beta band were mainly impaired in the left temporal region. The activity recorded by the MEG sensors mainly originates in the superficial neocortical temporal areas. Activity from the medial hippocampal and entorhinal cortex will have a much smaller amplitude at the scalp surface. However, both areas are strongly connected and abnormal temporal connectivity may reflect the primary pathology of the medial temporal lobe. Other MEG studies in AD have also stressed the importance of the (left) temporal region (Maestu et al., 2004, 2005). Left temporal disturbances have been associated with a higher chance of conversion to MCI (Maestu et al., 2006).

A surprising finding in the present study was the increase in SL and coherence of occipito-parietal connections and the right parietal region in the beta band and for coherence also in the alpha2 and gamma band. These regions may be relatively spared in the early stages of AD. Thus, it seems unlikely that this local increase in connectivity is due to loss of association fibers or lower acetylcholine levels. A possible, but at this stage highly speculative explanation could be that the parieto-occipital connectivity reflects a compensation mechanism in a relatively healthy part of the network. That the functional architecture of widespread brain networks can be influenced even at sites far away from local pathology has recently been demonstrated in patients with brain tumors (Bartolomei et al., 2006). Future studies will have to confirm the existence of the compensation mechanism and the possible influence of treatment on this phenomenon. More generally, it would be of interest to back up the correlations between impaired functional connectivity described in the present study by a more causal approach. The hypothesis is that the extent to which treatment with cholinesterase inhibitors or even rTMS restores normal functional connectivity would predict their favorable impact on cognitive functioning in AD.

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Appendix A. Mathematical background of synchronization likelihood

The synchronization likelihood (SL) is a measure of the *generalized synchronization* between two dynamical systems X and Y (Stam and van Dijk, 2002). Generalized synchronization (Rulkov et al., 1995) exists between X and Y of the state of the response system is a function of the driver system: $Y = F(X)$. The first step in the computation of the SL is to convert the time series X_i and Y_i recorded from X and Y as a series of state space vectors using the method of time delay embedding (Takens, 1982):

$$X_i = \left(X_i, X_{i+L}, X_{i+2\times L}, X_{i+3\times L} \ldots, X_{i+(m-1)\times L}\right) \quad (1)$$

where L is the time lag and m the embedding dimension. From a time series of N samples, $N-(m \times L)$ vectors can be reconstructed. State space vectors Y_i are reconstructed in the same way.

SL is defined as the conditional likelihood that the distance between Y_i and Y_j will be smaller than a cutoff distance r_y, given that the distance between X_i and X_j is smaller than a cutoff distance r_x. In the case of maximal synchronization, this likelihood is 1; in the case of independent systems, it is a small, but nonzero number, namely P_{ref}. This small number is the likelihood that two randomly

chosen vectors Y (or X) will be closer than the cut-off distance r. In practice, the cut-off distance is chosen such that the likelihood of random vectors being close is fixed at P_{ref}, which is chosen the same for X and for Y. To understand how P_{ref} is used to fix r_x and r_y, we first consider the correlation integral:

$$C_r = \frac{2}{N(N-w)} \sum_{i=1}^{N} \sum_{j=i+w}^{N-w} \theta\left(r - |X_i - X_j|\right) \quad (2)$$

Here, the correlation integral C_r is the likelihood that two randomly chosen vectors X will be closer than r. The vertical bars represent the Euclidian distance between the vectors. N is the number of vectors, w is the Theiler correction for autocorrelation (Theiler, 1986), and θ is the Heaviside function: $\theta(X) = 0$ if $X \geq 0$ and $\theta(\mathrm{X}) = 1$ if $X < 0$. Now, r_x is chosen such that $\mathrm{Cr}_x = P_{\mathrm{ref}}$ and r_y is chosen such that $\mathrm{Cr}_y = P_{\mathrm{ref}}$. The SL between X and Y can now be formally defined as:

$$\mathrm{SL} = \frac{2}{N(N-w)P_{\mathrm{ref}}} \times \sum_{i=1}^{N} \sum_{j=i+w}^{N-w} \theta\left(r_x - |X_i - X_j|\right)\theta\left(r_y - |Y_i - Y_j|\right) \quad (3)$$

SL is a symmetric measure of the strength of synchronization between X and Y ($\mathrm{SL}_{XY} = \mathrm{SL}_{YX}$). In Eq. (3), the averaging is done over all i and j; by doing the averaging only over j, SL can be computed as a function of time i. From Eq. (3), it can be seen that in the case of complete synchronization SL = 1; in the case of complete independence, SL = P_{ref}. In the case of intermediate levels of synchronization, $P_{\mathrm{ref}} < \mathrm{SL} < 1$.

In the present paper, the choice of the two most important embedding parameters L and m was based upon the frequency content of the time series (Montez et al., submitted for publication). L is chosen small enough to over-sample the highest frequencies present in the signal, and the embedding window $L \times m$ long enough to capture the period of the slowest frequency. For a given sample frequency in Hz and low frequency (LF) and high frequency (HF) filters in Hz, L (expressed in samples) is chosen such that L = sample frequency / (HF × 4). The embedding dimension m (expressed in samples) follows from: m = sample frequency / (LF × L). The Theiler correction w was chosen equal to the embedding window $L \times m$ and $P_{\mathrm{ref}} = 0.01$.

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