Neurophysiological signature(s) of visual hallucinations across neurological and perceptual

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CHAPTER 5

EEG-directed connectivity from posterior brain regions is decreased in dementia with Lewy bodies: a comparison with Alzheimer's disease and controls

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ABSTRACT

Directed information flow between brain regions might be disrupted in dementia with Lewy bodies (DLB) and relate to the clinical syndrome of DLB. To investigate this hypothesis, resting-state EEG recordings were obtained in patients with probable DLB and Alzheimer's disease (AD), and controls (N=66 per group, matched for age and gender). Phase transfer entropy (PTE) was used to measure directed connectivity in the groups for the theta, alpha and beta frequency band. A posterior-to-anterior PTE gradient, with occipital channels driving the frontal channels, was found in controls in all frequency bands. This posterior-to-anterior gradient was largely lost in DLB in the alpha band ($p<.05$). In the beta band, posterior brain regions were less driving in information flow in AD than in DLB and controls. In conclusion, the common posterior-to-anterior pattern of directed connectivity in controls is disturbed in DLB patients in the alpha band, and in AD patients in the beta band. Disrupted alpha band directed connectivity may underlie the clinical syndrome of DLB and differentiate between DLB and AD.

1. INTRODUCTION

Dementia with Lewy Bodies (DLB) is characterized by progressive cognitive decline in addition to fluctuating cognition (with pronounced deficits in attention), recurrent visual hallucinations and parkinsonism (McKeith et al., 2005). Diffuse deposition of Lewy bodies in the brain, particularly in the neocortex, has been associated with these core features of DLB (McKeith et al., 2005; Schneider et al., 2012). How this deposition of Lewy bodies leads to the clinical syndrome of DLB, remains unknown. One hypothesis is that structural alterations in parieto-occipital regions in DLB result in disrupted functional connectivity leading to the clinical syndrome of DLB (Borroni et al., 2015; Lee et al., 2010). Indeed, Peraza et al. found reduced fMRI functional connectivity in DLB between the fronto-parietal network in the left hemisphere, which also correlated with the severity and frequency of cognitive fluctuations (Peraza et al., 2014). Furthermore, reduced functional connectivity between the fronto-parietal network and the occipital lobe, but also within the occipital regions of the Default Mode Network (DMN) has been described in DLB (Lowther et al., 2014; Peraza et al., 2014). However, it is not only important to know whether structural and functional interactions are affected, but also if and to what extent the direction and strength of causal influences between brain regions is changed in DLB. Since attention is controlled by interaction between the top-down (goal-directed) dorsal and bottom-up (sensory stimulation) ventral fronto-parietal neural system of the brain (Corbetta and Shulman, 2002), attentional deficits in DLB could be caused by disruption in directed connectivity between the frontal and parietal brain regions involved in these attention networks.

There are no studies that examine directed connectivity in relation to attention in general in healthy subjects to test this hypothesis. However, various studies examining anesthesia-induced alterations in consciousness show that as the state of consciousness alters, changes in directed connectivity occur between the fronto-parietal (i.e. attentional) network. This state of unconsciousness is accompanied by a reversal in direction of information flow between brain regions that regains as consciousness recovers (Ku et al., 2011; Lee et al., 2013; Untergehrer et al., 2014). The tight relationship between attention and consciousness (Tsuchiya and Van Boxtel,

2013) suggests a potential role of disturbances in directed connectivity in attentional deficits as observed in DLB.

Quantitative electroencephalography (EEG) has shown to be a reliable method to measure correlates of cognitive fluctuations in DLB (Bonanni et al., 2008; McKeith et al., 2005; Walker et al., 2000). EEG directly measures neural activity, and its high temporal resolution closely reflects cognitive processes (Lopes da Silva, 2013). Recently, Van Dellen et al examined the EEG functional connectivity and network efficiency in DLB and found a less efficient network organization in this disorder (van Dellen et al., 2015). Altogether, different imaging techniques provide ample evidence of disrupted structural and functional connectivity in DLB (Lowther et al., 2014; Peraza et al., 2014; van Dellen et al., 2015). However, little is known about the exact changes in the directed information flow in DLB.

The present study aimed to investigate the directed connectivity in DLB patients with high temporal resolution EEG by using a novel phase-based measure for directed connectivity, Phase Transfer Entropy (PTE) (Lobier et al., 2014). PTE, a causal connectivity measure, provides an estimate for the strength and the direction of connectivity even in the presence of nuisance factors that accompany EEG recordings. Furthermore, PTE represents information flow not only specific to phase but also to frequency band (Lobier et al., 2014). First, information flow was investigated in controls to determine the normal pattern of information flow. Subsequently, the directionality was investigated in DLB patients to examine whether the information flow pattern is disturbed in this patient group, and whether this pattern correlates with attentional deficits in DLB. Patients with Alzheimer's disease (AD) were included as a second control group to explore the specificity of possible group differences to the pathophysiology of DLB.

2. METHODS

2.1 Study population

The EEG-dataset of the present study population has already been used for a different analysis focusing on the phase lag index and network topology in DLB and AD (van Dellen et al., 2015). Participants for this study were retrospectively selected from the Amsterdam Dementia Cohort from the Alzheimer Center of the VU University Medical Center (VUmc) in Amsterdam, The Netherlands (van Dellen et al., 2015). Subjects with cognitive complaints referred to the Alzheimer Center VUmc between September 2003 and June 2010 underwent a diagnostic assessment including neuropsychological assessment, brain magnetic resonance imaging (MRI), and resting state EEG, among others. The clinical data and test results of patients, who give informed consent, were stored in a local database and were available for research purposes (Van Der Flier et al., 2014). This general protocol for storage of clinical data was approved by the Medical Ethics Committee of the VUmc and was in agreement with the declaration of Helsinki. A clinical diagnosis and treatment plan were made by consensus in a weekly multidisciplinary meeting. Probable Alzheimer's disease was diagnosed according to the NINCDS-ADRDA criteria (McKhann et al., 1984) and probable dementia with Lewy Bodies was diagnosed according to Mckeith criteria (McKeith et al., 2005). Subjects were labeled as 'Subjective Cognitive Decline (SCD)' when they experienced and presented with cognitive complaints, but cognitive analysis was not aberrant and no other neurological or psychiatric disorder known to cause cognitive problems could be diagnosed (Van Der Flier et al., 2014). These subjects were included as a control group. Since diagnoses were made in the consensus meeting after clinical work-up, both patient groups, but also controls were using medication affecting the central nervous system (CNS). Since AD and DLB have distinctly different clinical and pathophysiological profiles (McKeith et al., 2005), the AD group was included as a second control group to explore differences specific to the DLB group. Each diagnostic group consisted of 66 subjects, matched on group level for age and gender.

2.2 Neuropsychological assessment

Cognitive functions in the diagnostic work-up in the Alzheimer Center VUmc were assessed using a standardized test battery (Van Der Flier et al., 2014). From this, the Mini-Mental State Examinations (MMSE) was used as a measure of global cognitive decline (Folstein et al., 1975), the Trail Making Test part A as a measure of motor speed (Reitan, 1958), and the TMT test part B (TMT-B) and the forward and backward condition of the Digit Span (Lindeboom and Matto, 1994) as a measure of attention. TMT-B measures cognitive flexibility, which refers to the mental ability to shift one's thinking or attention between tasks or environmental stimuli (Miyake et al., 2000). However, TMT-B has also been associated with the cognitive domain attention (Crowe, 1998; Oosterman et al., 2010; Reitan, 1992). TMT-A and TMT-B is measured in seconds to complete the task so that high test scores correspond to worse task performance.

2.3 EEG recordings

As previously described, as part of the diagnostic work up, all subjects underwent a 20-minutes no-task, resting-state EEG recording with OSG digital equipment (Brainlab®; OSG B.V. Belgium) (van Dellen et al., 2015). Twenty-one electrodes were placed on the scalp according to the international 10-20 system recorded on the following locations: Fp2, Fp1, F8, F7, F4, F3, A2, A1, T4, T3, C4, C3, T6, T5, P4, P3, O2, O1, Fz, Cz, Pz. The sample frequency was 500 Hz. Electrode impedance was below 5kΩ with a time constant of 1s and a low pass filter at 70 Hz. For recordings, patients were seated in a slightly reclined chair in a sound attenuated room and kept awake by EEG technicians with sound stimuli if necessary (Van Der Flier et al., 2014). Two authors (EvD, HdW) visually selected four artifact-free epochs, recorded in an awake state with eyes closed, for each subject. Data were converted to ASCII format, and 4 epochs of 4096 samples per subject (i.e. approximately 4*8 sec EEG data per subject, sufficient to perform quantitative EEG analyses (Gasser et al., 1985)) were loaded into the BrainWave software for further analysis (BrainWave version 0.9.151.5, C. J. Stam; available for download at http:/home.kpn.nl/stam7883/brainwave.html). EEG source derivation was used as reference (Hjorth, 1975) and the data was band-pass filtered in three frequency bands: theta (4-8 Hz), alpha (8-13 Hz), and beta (13-30 Hz).

Oscillations under 4 Hz and above 30 Hz were not analyzed because of the expected contamination with eye movement (Hagemann and Naumann, 2001), muscle artifacts and microsaccades (Whitham et al., 2007).

2.4 Directed connectivity analysis

Phase transfer entropy (PTE) was used as a measure for directed connectivity between EEG channels. PTE measures the strength and direction of phase-based functional connectivity between interacting oscillations. PTE was introduced by Lobier et al (Lobier et al., 2014) and is based on the principle of Transfer Entropy (TE) (Schreiber, 2000). TE measures whether predicting the future of a target signal Y is improved when the past of source signal X is included as additional information to the already known past of target signal Y, compared to the situation when only the past of target signal Y is known (Schreiber, 2000). Basically, TE quantifies the difference between the amount of two mutual information values necessary to transfer information from signal X to signal Y (Schreiber, 2000):

$$\mathrm{TE}_{xy} = \sum p(\mathrm{Y}_{t+\delta}, \mathrm{Y}_t, \mathrm{X}_t) \log\left(\frac{p(\mathrm{Y}_{t+\delta} \mid \mathrm{Y}_t, \mathrm{X}_t)}{p(\mathrm{Y}_{t+\delta} \mid \mathrm{Y}_t)} \right),$$

Interestingly, TE can also be estimated from the instantaneous phase time-series of signal X and Y, as was done by Lobier et al to create the PTE (Lobier et al., 2014):

$$\mathrm{PTE}_{xy} = \sum p(\mathrm{Y}_\delta)\, p(\mathrm{Y})\, p(X) \log\left(\frac{p(\mathrm{Y}_\delta \mid \mathrm{Y}, \mathrm{X})}{p(\mathrm{Y}_\delta \mid \mathrm{Y})} \right)$$

For this study, normalized PTE, as described in Hillebrand et al (Hillebrand et al 2015, in press), was used:

$$\mathrm{dPTE}_{xy} = \frac{\mathrm{PTE}_{xy}}{\mathrm{PTE}_{xy} + \mathrm{PTE}_{yx}}$$

dPTE indicates which signal is a directional driver and which signal is a directional receiver of information. dPTE value ranges between 0 and 1. When a signal X is driving more strongly with respect to signal Y than the other way around, the value for dPTE is $0.5<dPTE\leq1$. When signal X is receiving with respect to signal Y, $0\leq dPTE<0.5$. In case where the information flow between signal X and signal Y is balanced, dPTE = 0.5. See supplementary material and Hillebrand et al. for a detailed explanation of the dPTE (Hillebrand et al 2015, in press).

In order to compare dPTE values between the three subject groups, dPTE value for all pairs of EEG channels were computed for all the four epochs for each frequency band for all the subjects, and subsequently averaged per EEG channel. Subsequently, for each frequency band, the computed dPTE values for all the four epochs per subject were averaged over the four epochs to compute one average dPTE value per EEG channel to all other channels (= defined as mean dPTE).

2.5 Statistical analysis

Brainwave software was used to compute the averaged dPTE value per EEG channel to all other channels for all the four epochs for each frequency band for all the subjects. Subsequently, statistical analyses were performed using IBM SPSS Statistics 23. Neuropsychological test scores at baseline were compared between groups using univariate ANOVA, and medication use (defined as the number of subjects using any medication affecting the CNS) was compared using the Pearson Chi square test. The alpha was considered significant at the level of .05.

The dPTE data per EEG channel, and the data of the neuropsychological tests were not normally distributed. Therefore, the mean dPTE between the three groups was compared using non-parametric Kruskal-Wallis test with False Discovery Rate (FDR) approach with adjusted p-value (i.e. q-value) of .05 to correct for multiple comparisons. Afterwards, post-hoc analyses were done using pair wise Mann-Whitney U test. Additionally, to investigate the earlier mentioned hypothesis of a potential correlation between attention and posterior brain regions, Spearman's rho correlation was used to test whether mean dPTE in the posterior brain regions (i.e. EEG channels T5-T6-

P3-P4-Pz-O1-O2) was related to TMT-B test in DLB patients ($p<.05$). Furthermore, to explore the specificity of a possible correlation between directed connectivity in the posterior brain regions and attention in DLB, a Spearman's rho correlation was also calculated for mean dPTE in the posterior brain regions, and MMSE and TMT-A test in DLB patients ($p<.05$). This was done for each frequency band separately.

3. RESULTS

3.1 Patient Characteristics

The patient characteristics are shown in Table 1. The groups were matched for age, sex and level of education and therefore showed no differences in these variables. DLB patients showed lower mean MMSE compared to the control group, while their scores were higher compared to AD patients ($p<.05$). In contrast, DLB patients performed the worst on the TMT-A task and experienced more hallucinations compared to the other two groups ($p<.05$). The use of medication affecting the CNS was highest in the DLB group ($p<.05$) (van Dellen et al., 2015).

Table 1: Patient characteristics

	DLB	AD	Control
n	66	66	66
Age, yrs	70 (9)	70 (9)	70 (7)
Sex, female	14 (21%)	14 (21%)	14 (21%)
Disease duration, yrs	2.9 (2.2)	3.3 (2.2)	3.6 (4.8)
MMSE[a]	23(5) (n=59)	21 (5) (n=63)	28 (1) (n=66)
VAT[a]	7.9 (3.5) (n=47)	5.6 (4.3) (n=60)	11.5 (.8) (n=62)
TMT-A[a], sec TMT-B, sec	123 (86) (n=47) 412.6 (223.1) (n=36)	87 (63) (n=54) NA	43 (15) (n=63) NA
Digit Span forward[b]	11.5 (2.5) (n=50)	10.5 (3.2) (n=61)	12.4 (3.0) (n=64)
Digit Span backward[c]	6.5 (2.8) (n=49)	6.6 (3.0) (n=60)	9.3 (2.9) (n=64)
Hallucinations[a]	16 (24.2%)	3 (4.5%)	0 (0%)
CNS medication[d,e]	16 (24.2%)	6 (9.1%)	6 (9.1%)
Rivastigmine	6 (9.1%)	4 (6.1%)	1 (1.5%)
Haloperidol	1 (1.5%)	1 (1.5%)	1 (1.5%)
Clozapine	2 (3%)	0 (0%)	0 (0%)
Quetiapine	2 (3%)	0 (0%)	0 (0%)
AED	3 (4.5%)	1 (1.5%)	2 (3%)
Other CNS medication	3 (4.5%)	0 (0%)	2 (3%)

Data are mean (SD) or n (%). Disease duration measured as years since onset of complaints. TMT-A and TMT-B scores are presented as time needed to complete the task; higher scores mean worse performance. Diagnoses, including 'subjective cognitive decline' for the control group, were made in a consensus meeting after clinical work-up; therefore, some control subjects were using medication affecting the central nerve system. Hallucinations were assessed using the Neuropsychiatric Inventory (NPI).

Key: AD: Alzheimer's disease; AED: Anti-Epileptic Drugs; CNS: central nerve system; DLB: Dementia with Lewy Bodies; MMSE: Mini Mental State Examination; NA: Not Available; SD: standard deviation; sec: seconds; TMT-A: Trail Making Test part A; TMT-B: Trail Making Test part B; VAT: Visual Association Test; yrs: years

[a] Significantly different between all groups ($p<.05$)

[b] Significantly different between AD and controls

[c] Significantly different between the two dementia groups and controls ($p<.05$)

[d] Significantly different between DLB and controls ($p<.05$)

[e] Significantly different between AD and DLB ($p<.05$)

3.2 Directed connectivity analysis

3.2.1 Control group

First, the mean dPTE per EEG channel (= average dPTE value per EEG channel to all other channels) was examined in the theta, alpha and beta frequency band in the control group. The control group showed a posterior-to anterior pattern of information flow, with relatively high dPTE values in the posterior part of the brain, and relatively low dPTE values in the frontal part of the brain (figure 1). This dPTE distribution pattern indicates that occipital regions drive the frontal regions. This pattern was most evident in the alpha band (figure 1a), but was also distinguishable in the beta (figure 2a), and theta band (figure S2a).

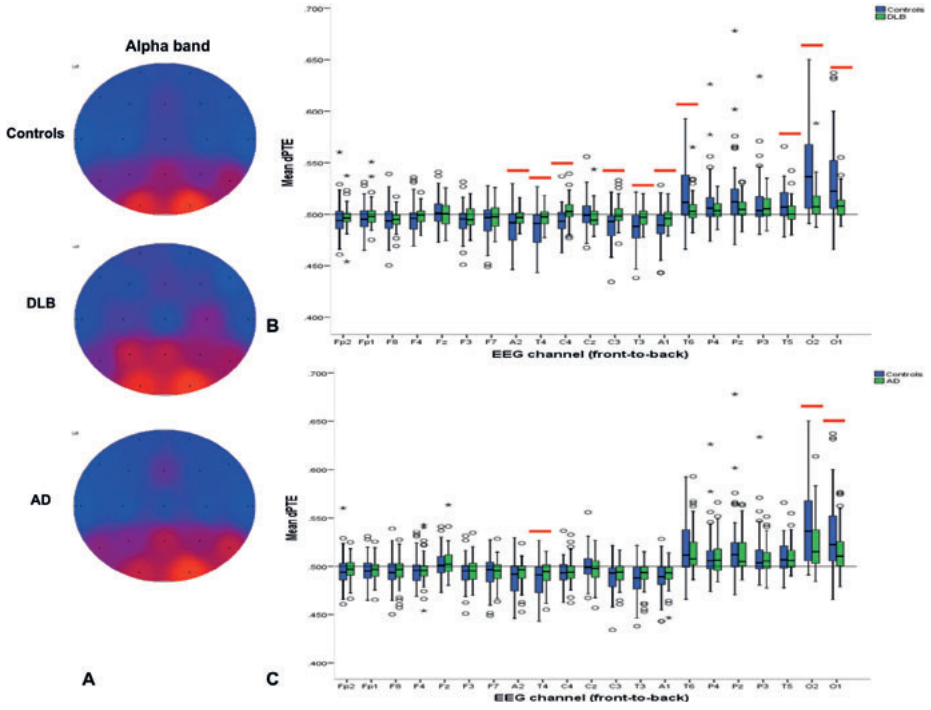

Figure 1. (A) Topological representation of mean dPTE per group in the alpha band. Orientation: nose up, left is left hemisphere. Red: relatively high dPTE value (dPTE>0.5); blue: relatively low dPTE value (dPTE<0.5). Note: the colors show a relative dPTE value within the group. Blue in one map does not necessarily indicate the same dPTE value in another map. AD: patients with Alzheimer's disease. DLB: patients with Dementia with Lewy Bodies. **(B)** Boxplots showing mean dPTE in controls and DLB patients in the alpha band. Blue and green colors represent controls and DLB patients, respectively. **(C)** Boxplots showing mean dPTE in controls and AD patients in the alpha band. Blue and green colors represent controls and AD patients, respectively. X-axis: EEG channels shown from frontal to occipital. Y-axis: mean dPTE of each EEG channel to all other channels. Red lines indicate significant difference in mean dPTE for a particular EEG channel between a patient group and controls, tested with non-parametric Kruskal-Wallis test with FDR approach to correct for multiple comparisons ($p<.05$).

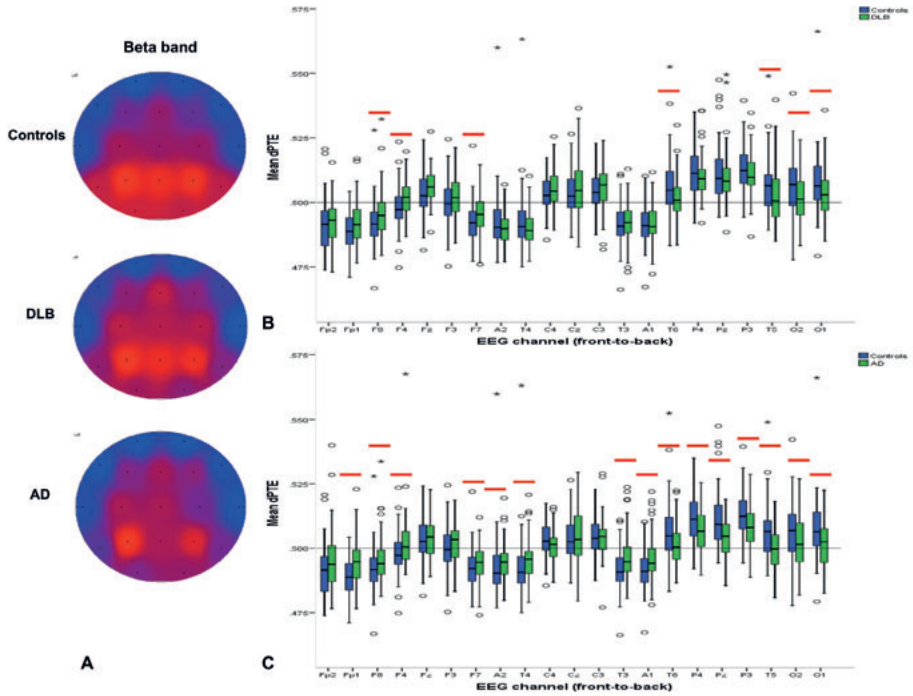

Figure 2. (A) Topological representation of mean dPTE per group in the beta band. Orientation: nose up, left is left hemisphere. Red: relatively high dPTE value (dPTE>0.5); blue: relatively low dPTE value (dPTE<0.5). Note: the colors show a relative dPTE value within the group. Blue in one map does not necessarily indicate the same dPTE value in another map. AD: patients with Alzheimer's disease. DLB: patients with Dementia with Lewy Bodies. **(B)** Boxplots showing mean dPTE in controls and DLB patients in the beta band. Blue and green colors represent controls and DLB patients, respectively. **(C)** Boxplots showing mean dPTE in controls and AD patients in the beta band. Blue and green colors represent controls and AD patients, respectively. X-axis: EEG channels shown from frontal to occipital. Y-axis: mean dPTE of each EEG channel to all other channels. Red lines indicate significant difference in mean dPTE for a particular EEG channel between a patient group and controls, tested with non-parametric Kruskal-Wallis test with FDR approach to correct for multiple comparisons ($p<.05$).

3.2.2. Controls vs. disease groups

In the alpha band, AD patients showed the same characteristic posterior-to-anterior dPTE pattern as controls (figure 1a), whereas in DLB patients, this characteristic posterior-to-anterior pattern was disturbed showing a dPTE gradient shift from posterior towards anterior (figure 1a). The mean differences in dPTE between the two dementia groups and controls in the alpha band are shown in figure 1b and 1c. In the alpha band, occipital channels in controls were more driving compared to occipital channels in the two patient groups ($p<.05$; figure 1b and 1c). In addition, differences were found between the DLB group and controls in the central and temporal channels ($p<.05$; figure 1b). These differences in mean dPTE between DLB patients and controls indicated a loss of PTE gradient in DLB patients with mean dPTE approaching the value of .50 (figure 1b).

In the beta band, the occipital channels in controls were again more driving compared to the disease groups ($p<.05$; figure 2b and 2c). Comparing the two patient groups with controls showed that differences in mean dPTE in the beta band between AD patients and controls (figure 2c) were greater than between DLB patients and controls (figure 2b). In the posterior part of the brain, channels were more driving in controls, while in the frontal part of the brain, channels were more driving in AD patients ($p<.05$; figure 2c).

In the theta band, DLB patients and controls differed in mean dPTE at electrode P3 and T5 ($p<.05$; figure S2b), whereas AD patients and controls differed only at electrode P3 ($p<.05$; figure S2c).

3.3.3. DLB vs. AD

In the alpha band, differences in mean dPTE were found in the occipital, and centro-temporal channels between DLB and AD patients ($p<.05$; figure S1c), whereas in the beta band only the centro-temporal channels showed difference in mean dPTE between the two disease groups ($p<.05$; figure S1d). Comparing the two patient groups in the theta band resulted in difference in mean dPTE only at electrode T5 ($p<.05$; figure S2d).

3.3 Directed connectivity and neuropsychological tests in DLB

A higher mean dPTE in the posterior brain regions in the beta band correlated with better performance on the TMT-B test in DLB patients (N=36, ρ=-.37; p=.03). No correlations were found between performance on TMT-B test and mean dPTE in the posterior brain regions in the theta and alpha band. Moreover, no correlations were found between performance on MMSE, forward Digit Span, backward Digit Span, and TMT-A test, and mean dPTE in the posterior brain regions in none of the frequency bands.

4. DISCUSSION

4.1 Main findings

The present study provides evidence that in controls information flow between brain regions is directed from posterior-to-anterior in the theta, alpha, and beta frequency band during an eyes-closed wakeful resting-state condition. In controls, this flow direction is most prominent in the alpha band. This typical pattern is also evident in EEG recordings of AD patients in the alpha band. Interestingly, comparing DLB patients to controls showed that in DLB patients, the directed connectivity in the alpha band is disturbed and shows a loss of dPTE gradient representing a less pronounced pattern of posterior-to-anterior information flow. In the beta band, disturbance in directed connectivity is more pronounced in the AD patient group. Posterior brain regions in the beta band are far less driving in information flow in AD patients than in DLB patients and controls.

Analysis of directed connectivity in relation to attentional deficits in DLB showed that higher mean dPTE in the posterior brain regions in the beta band correlates with better performance on the TMT-B test.

4.2 Impaired directed connectivity in DLB

The findings of the present study support previous results regarding the possibly predisposing role of posterior brain regions in the pathophysiology of DLB (Bonanni et al., 2008; Galvin et al., 2011; Kenny et al., 2012; Lowther et al., 2014; Peraza et al.,

2014). Furthermore, Franciotti et al. investigated the DMN activity in 18 DLB and 18 AD patients, and found evidence for directed information flow from posterior to anterior in both hemispheres in AD patients, while in DLB this was only the case in the left hemisphere. In DLB, causal influence in the right hemisphere was directed from the middle frontal gyrus to the lateral parietal cortex and showed a correlation with the severity of cognitive fluctuations (Franciotti et al., 2013). These findings suggest a potential role of disrupted directed connectivity in the etiology of the core symptoms of DLB. However, fMRI has limited temporal resolution, and does not measure neural activity directly (Logothetis et al., 2001). The present results, however, provide strong support for the hypothesis that directed connectivity in DLB is mainly impaired at parieto-occipital electrodes, possibly due to underlying abnormalities in the posterior areas of the brain. Notably, DLB patients show no reversal in the pattern of directed connectivity. As aforementioned, Van Dellen et al showed that network organization in DLB is less efficient. This network inefficiency was characterized by a loss of functional hubs (highly connected network nodes) and lower alpha band functional connectivity strength compared to controls (van Dellen et al., 2015). These results suggest that hubs (predominantly located in the posterior part of the healthy brain (Van den Heuvel and Sporns, 2013; Moon et al., 2015)) in general in both healthy subjects and dementia, might be the directional source that drives connected brain areas. Therefore, loss of these hubs in DLB can be the cause of lower connectivity strength and decreased directional lead as found in the present study. In addition, this impaired brain network organization is supported by the recently described regular network topology in DLB by Peraza et al (Peraza et al., 2015). Peraza et al found loss of long-distance connections (possibly long fibers that join posterior areas to frontal areas) in the fMRI brain networks of DLB patients, while short-range connections were increased, resulting in higher local connectivity and more dissociated functional brain modules. Moreover, these network alterations were correlated with the degree of cognitive fluctuations (measured with the Clinical Assessment of Fluctuating Confusion scale) in DLB (Peraza et al., 2015). As changes in the brain network organization of the brains of AD patients have been shown to result in loss of small-worldness, and redistribution of hubs, which in turn is associated with cognitive deficits in AD (Xie and

He, 2012), all the above mentioned findings suggest that alterations in brain network organization might also relate to the underlying mechanism in the pathophysiology of DLB. These network disturbances may lead to disrupted causal interactions between brain regions, which in turn might result in impaired brain functioning and thus possibly in the clinical syndrome of DLB.

4.3 Directed connectivity & cognitive fluctuations

As described earlier, contradicting findings have been reported about the relationship between impaired functional connectivity between frontal and parietal brain areas, and cognitive fluctuations (Franciotti et al., 2013; Lowther et al., 2014; Peraza et al., 2014). The present study aimed to investigate causal interactions between brain regions in relation to attentional deficits in DLB. For this, TMT-B, and Digit Span tests were used as a measure for attention. Digit span is used to measure working memory (Richardson, 2007). TMT-B measures cognitive flexibility, but various studies provide evidence that TMT-B is related to the cognitive domain attention, among others (Crowe, 1998; Oosterman et al., 2010). The significant correlation between mean dPTE and TMT-B suggests that DLB patients fail in the mental ability of *shifting attention* between tasks or environmental stimuli, a core deficit in DLB. It could have been expected that impaired directed connectivity in the alpha band should show a stronger correlation with attentional deficits in DLB, because the most pronounced differences in dPTE compared to controls were found in this frequency band. As the association between TMT-B and directed connectivity is found in a different frequency band than the main group difference with controls, these contrastive results indicate the complexity of the pathophysiology of attentional deficits in DLB.

Although alpha oscillations play a key role in (visual) attention (Lopes da Silva, 2013), beta band oscillations have also been associated with increased alertness showing higher EEG activation in the beta band over parieto-occipital regions preceding visual stimuli (Kamiński et al., 2012). Moreover, Kopell et al showed in a simulation study that beta band oscillations have synchronization properties that are suitable for long distance interactions (N Kopell et al., 2000). In addition, a magnetoencephalography (MEG) study in humans revealed that beta band phase synchronization is involved in

communication in fronto-parietal network during attention tasks (Gross et al., 2004). These findings suggest a key role of the beta band in mediating interactions in the fronto-parietal attentional network, and hints that impaired directed connectivity between frontal and parietal brain areas in the beta band might be related to the pathophysiological mechanism of attentional deficits in DLB, though is not a complete explanation. Though, a replication of this study with functional imaging techniques like MEG with better temporal and spatial resolution than EEG (Cromarty et al., 2015; Lopes da Silva, 2013), should be performed to evaluate the exact role of directed connectivity in the beta band in the pathophysiology of attentional deficits in DLB.

4.5 Directed connectivity in Alzheimer's disease

In the beta band, AD patients showed more diffuse significant changes in directed connectivity compared to controls. In the posterior part of the brain, channels were significantly more driving in controls, while in the frontal part of the brain, channels were significantly more driving in AD patients. Interestingly, this pattern did not occur in DLB patients and thus indicates a beta band change specific to AD patients. The directed connectivity pattern of AD patients in the alpha band was nearly similar to the directed connectivity pattern of controls, except for the occipital channels where the AD group was less driving with regard to controls. These findings are in line with previous work that shows slowing of the dominant occipital rhythm in AD (Kwak, 2006), and shift of alpha and beta activity from posterior towards more frontal regions (Babiloni et al., 2009; de Waal et al., 2012; Engels et al., 2015). Additionally, previous EEG and MEG studies report decreased functional connectivity in AD in the alpha and beta band (Stam et al., 2009, 2005). Furthermore, AD is increasingly considered as a hub vulnerability disease (Buckner et al., 2009; Engels et al., 2015; Tijms et al., 2013). Recently, Engels et al (Engels et al., 2015) described that functional connectivity in AD decreases in the posterior brain regions with increasing AD severity, and that hub location in AD gradually shift from posterior to more central brain regions (Engels et al., 2015). Since (a part of) brain hub regions show a striking overlap with the DMN (i.e. precuneus/posterior cingulate among others) (Buckner et al., 2009), the results of the present study may indicate that the causal influence of posterior DMN structures

on other parts of the brain is decreased in AD. This hypothesis is in line with previous reports of DMN dysfunction, and diminished anterior-posterior integration of the DMN in AD (Greicius et al., 2004; Toussaint et al., 2014).

4.6 Strengths & Limitations

A strength of this study is that it compares a relatively large DLB group with carefully matched controls and AD patients. In addition, this study made use of PTE as a measure of directed connectivity, which is not only resistant to EEG nuisance parameters as noise and linear mixing, but also insensitive to EEG reference (Lobier et al., 2014). This makes PTE a robust measure for directed connectivity.

This study also has some limitations. First, the low spatial resolution of (21-channel) EEG makes it difficult to examine specific anatomical regions. However, the aim of the present study was to globally measure the directed connectivity in the brain, which can be well studied using EEG recordings (Lopes da Silva, 2013). It would be interesting to study the role of directional connectivity in specific areas in DLB by using MEG (Hillebrand et al., 2012). Second, the higher use of medication affecting CNS in DLB might have influenced the results of attentional deficits. However, the majority of the DLB patients (>75%, Table 1) did not use any medication acting on the CNS. Besides, the mean dPTE value in the posterior brain regions in the three frequency bands did not differ between DLB patients with and without CNS medication (theta: $t(64) = .06$, $p=.95$; alpha: $t(64) = 1.78$, $p=.08$; beta: $t(64) = .37$, $p=.72$). Third, quantitative measures of the extent and severity of motor deficits were not available in DLB patients to analyze possible correlations between parkinsonism and directed connectivity patterns. However, a global qualitative measure of parkinsonism (i.e. presence of parkinsonism) was available in a small subgroup (26 out of 66 patients), but showed no correlation with directed connectivity patterns (alpha: $\rho=.32$, $p=.11$; beta: $\rho=-.08$, $p=.72$). In Parkinson's disease, a modest correlation has been shown between connectivity and motor symptoms (Olde Dubbelink et al., 2013b). This could not be replicated in the present study. Therefore, future studies are needed to elucidate the relationship between connectivity patterns and motor symptoms in DLB. Fourth, this study used subjects with SCD as a control group. These subjects visited the memory

clinic with subjective memory complaints, and therefore represent a heterogeneous group. Therefore, larger disease effects might have been found if a healthy control group was included. In 11 SCD subjects, the clinical diagnosis was converted at follow-up (range 0 – 7 years). From this, 6 subjects were converted to Mild Cognitive Impairment (MCI), 3 were converted to AD, one to vascular dementia, and one to Parkinson's disease. However, the clinical work-up at baseline in this group was not aberrant and therefore the clinical profile of the control group represents the clinical profile of a healthy population. In fact, in the clinical practice, this group is the exact population from which patients with a diagnosis of dementia need to be distinguished. Finally, several studies report extensive pathological overlap between DLB and AD by showing overlap in the anatomical distribution of hallmark neuropathological lesions (Chung et al., 2015; L. Walker et al., 2015), whereas the present study shows difference in brain functioning between these two forms of dementia. These contrastive findings of structural and functional brain abnormalities in AD and DLB suggest that the pathophysiological difference between DLB and AD might be underestimated.

5. CONCLUSION

This study showed that the posterior-to-anterior pattern of directed connectivity commonly seen in controls is disturbed in DLB patients in the alpha band, and in AD patients in the beta band. Disrupted information flow in DLB, possibly caused by brain network disturbances, may relate to the clinical syndrome of DLB. Future studies with neuroimaging tools with higher temporal and spatial resolution such as MEG are needed to explore the specific pathophysiological role of directed connectivity in various anatomical regions in DLB.

SUPPLEMENTAL MATERIAL

Results

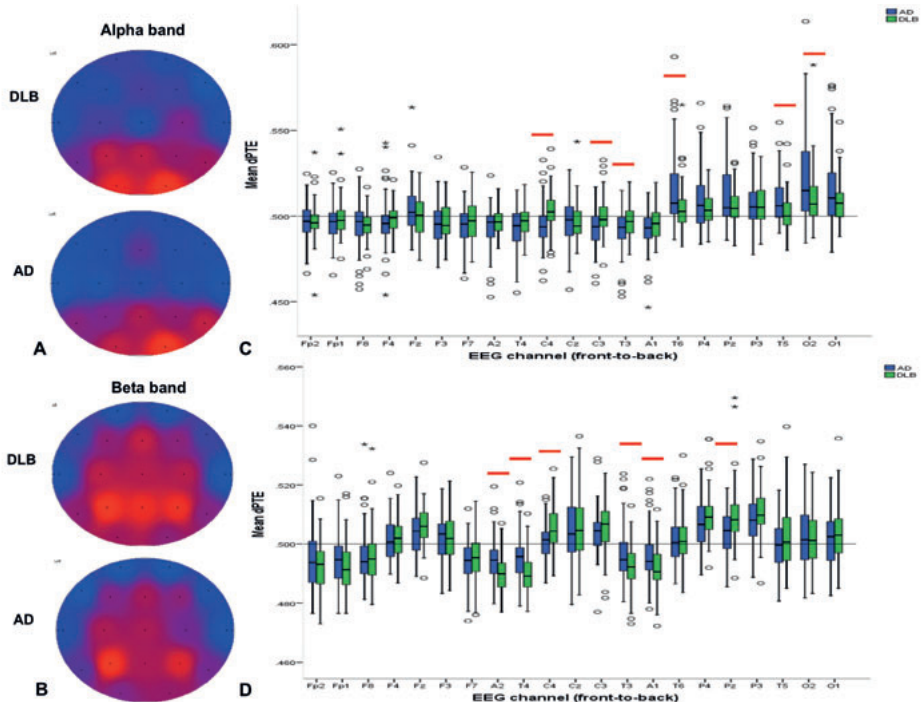

Figure S1. (A and B) Topological representation of average dPTE in DLB and AD patients in the alpha and beta band, respectively. Orientation: nose up, left is left hemisphere. Red: relatively high dPTE value (dPTE>0.5); blue: relatively low dPTE value (dPTE<0.5). Note: the colors show a relative dPTE value within the group. Blue in one map does not necessarily indicate the same dPTE value in another map. AD: patients with Alzheimer's disease, DLB: patients with Dementia with Lewy Bodies. (**C)** Boxplots showing mean dPTE in AD and DLB patients in the alpha band. Blue and green colors represent AD and DLB patients, respectively. **D:** Boxplots showing mean dPTE in AD and DLB patients in the beta band. Blue and green colors represent AD and DLB patients, respectively. X-axis: EEG channels shown from frontal to occipital. Y-axis: mean dPTE of each EEG channel to all other channels. Red lines indicate significant difference in mean dPTE for a particular EEG channel between the two patient groups, tested with non-parametric Kruskal-Wallis test with FDR approach to correct for multiple comparisons ($p<.05$).

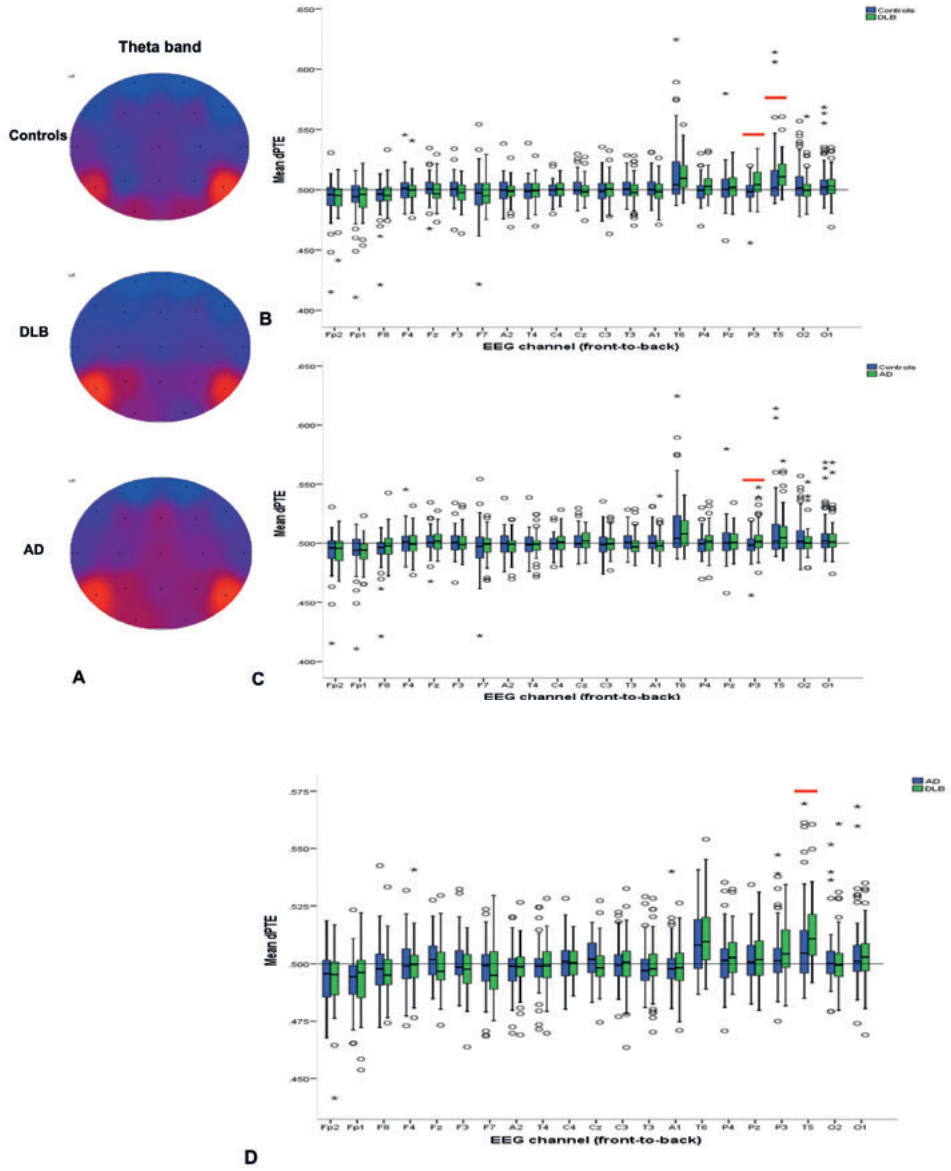

Figure S2. (A) Topological representation of mean dPTE per group in the theta band. Orientation: nose up, left is left hemisphere. Red: relatively high dPTE value (dPTE>0.5); blue: relatively low dPTE value (dPTE<0.5). Note: the colors show a relative dPTE value within the group. Blue in one map does not necessarily indicate the same dPTE value in another map. AD: patients with Alzheimer's disease. DLB: patients with Dementia with Lewy Bodies.

(**B)** Boxplots showing mean dPTE in controls and DLB patients in the theta band. Blue and green colors represent controls and DLB patients, respectively. (**C)** Boxplots showing mean dPTE in controls and AD patients in the theta band. Blue and green colors represent controls and AD patients, respectively. (**D)** Boxplots showing mean dPTE in AD and DLB patients in the theta band. Blue and green represent AD and DLB patients, respectively. X-axis: EEG channels shown from frontal to occipital. Y-axis: mean dPTE of each EEG channel to all other channels. Red lines indicate significant difference in mean dPTE for a particular EEG channel between a patient group and controls, tested with non-parametric Kruskal-Wallis test with FDR approach to correct for multiple comparisons ($p<.05$).