Psychiatry Research: Neuroimaging 222 (2014) 91–99

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Functional connectivity in major depression: Increased phase synchronization between frontal cortical EEG-source estimates

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ARTICLE INFO

Article history:
Received 23 July 2013
Received in revised form
28 November 2013
Accepted 19 February 2014
Available online 26 February 2014

Keywords:
eLORETA
Nonlinear lagged coherence
Antidepressant medication
Dorsolateral prefrontal cortex
Subgenual prefrontal cortex
Medial prefrontal cortex

ABSTRACT

Structural and metabolic alterations in prefrontal brain areas, including the subgenual (SGPFC), medial (MPFC) and dorsolateral prefrontal cortex (DLPFC), have been shown in major depressive disorder (MDD). Still it remains largely unknown how brain connectivity within these regions is altered at the level of neuronal oscillations. Therefore, the goal was to analyze prefrontal electroencephalographic phase synchronization in MDD and its changes after antidepressant treatment. In 60 unmedicated patients and 60 healthy controls (HC), a 15-min resting electroencephalogram (EEG) was recorded in subjects at baseline and in a subgroup of patients after 2 weeks of antidepressant medication. EEG functional connectivity between the SGPFC and the MPFC/DLPFC was assessed with eLORETA (low resolution brain electromagnetic tomography) by means of lagged phase synchronization. At baseline, patients revealed increased prefrontal connectivity at the alpha frequency between the SGPFC and the left DLPFC/MPFC. After treatment, an increased connectivity between the SGPFC and the right DLPFC/MPFC at the beta frequency was found for MDD. A positive correlation was found for baseline beta connectivity and reduction in scores on the Hamilton depression rating scale. MDD is characterized by increased EEG functional connectivity within frontal brain areas. These EEG markers of disturbed neuronal communication might have potential value as biomarkers.

1. Introduction

Major depressive disorder (MDD) is a severe and life-threatening disorder. Although the underlying pathomechanisms are yet to be understood, the prefrontal cortex (PFC), including the subgenual prefrontal cortex (SGPFC), the medial prefrontal cortex (MPFC) and the dorsolateral prefrontal cortex (DLPFC), has been a focus of research (Price and Drevets, 2010, 2012). These brain areas have been associated with the identification of emotional stimuli and affective response regulation (Phillips et al., 2003), reward processing (Pochon et al., 2002; Liu et al., 2011) and experience of negative mood states or transient sadness (Mayberg et al., 1999; Lévesque et al., 2011); a prefrontal dysfunction is thought to account for core symptoms of depression such as anhedonia and cognitive deficits (Pizzagalli et al., 2004; Diener et al., 2012; Duman and Aghajanian, 2012). Structural imaging studies have shown altered in vivo cortical volume in MDD in prefrontal areas, including the SGPFC with decreased grey matter volume (Drevets et al., 1997; van Tol et al., 2010) and the DLPFC with reduced in vitro neuronal cell size and decreased glial cell density (Cotter et al., 2002).

These findings are paralleled by metabolic alterations revealed by positron emission tomography (PET) studies that show, for example, decreased glucose metabolism in prefrontal areas such as the SGPFC (Drevets et al., 1997; Pizzagalli et al., 2004). Functional magnetic resonance imaging (fMRI) studies have revealed a primarily prefrontal focus of altered blood-oxygen-level-dependent (BOLD) signals in MDD compared with healthy controls (Lemogne et al., 2012), while the SGPFC has been found to yield increased fMRI-based functional connectivity patterns within the default mode network (Greicius et al., 2007) and the dorsomedial prefrontal cortex (Davey et al., 2012). Recently, the BOLD-signal time courses at the left DLPFC, a location shown to be the most clinically efficacious target in transcranial magnetic stimulation (TMS) treatment, were found to be negatively correlated with the BOLD signal of the SGPFC, underpinning the value of connectivity analysis (Fox et al., 2012a).

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http://dx.doi.org/10.1016/j.pscychresns.2014.02.010
0925-4927

Table 1
Shown are sociodemographic features for patients with major depressive disorder (MDD) and healthy controls (HC) of the whole sample and the subsample with re-assessment of connectivity after 14 days of medication with an antidepressant.

	Whole sample MDD ($n=60$)	Whole sample HC ($n=60$)	p-value
Age (years ± SD)	39.41 ± 13.32	37.3611.38	T-test $p=0.37$
Gender	34 female	30 female	Chi²-test $p=0.46$
HRDS-21 (score ± SD)	19.78 ± 6.18		
	Sample retest MDD ($n=21$)	Sample retest HC ($n=23$)	p-value
Age (years ± SD)	42.38 ± 15.33	37.57 ± 10.38	T-Test $p=0.20$
Gender	11 female	10 female	Chi²-test $p=0.56$
HRDS-21 baseline (± SD)	17.48 ± 5.21		
HRDS-21 14 days (± SD)	9.86 ± 4.44		
Medication	Escitalopram $n=15$ (10–20 mg)		
	Mirtazapine $n=6$ (15–30 mg)		

MDD is characterized by disturbed emotional processing (Diener et al., 2012). Findings from EEG-connectivity studies that used paradigms with emotional stimuli have shed light on the underlying electrophysiological connectivity patterns during emotional processing in healthy subjects. In particular, alterations within the beta frequency band have been associated with emotional stimuli. For example, increased EEG coherence, as a measure of functional connectivity, has been found during emotional stimulation (Miskovic and Schmidt, 2010), while a decrease in beta coherence has been associated with reduced control over emotional information in healthy subjects (Reiser et al., 2012). Besides this evidence for the association between EEG coherence and emotional processing, characteristic alterations that mainly involve increased coherence have also been reported during the resting state in MDD: Fingelkurts et al. (2007) found increased synchronization in the EEG alpha and theta bands in patients with MDD, and Leuchter et al. (2012) recently reported an increased topographic EEG coherence between frontal brain areas in MDD in the EEG alpha, beta and theta bands. Further Lee et al. (2011) found that responders to antidepressant treatment, compared with non-responders, showed increased coupling of EEG power at the delta and theta frequencies between right fronto-parietal electrodes.

To bring together findings of structural and metabolic alterations with reports of increased topographical electrophysiological coherence in MDD, the goal of this study was to explore EEG-based phase synchronization as a measure of electrophysiological brain connectivity between anatomical structures such as the SGPFC and other prefrontal brain areas including the DLPFC and the MPFC in MDD patients in comparison to healthy controls (HC) under resting conditions. Therefore, region of interest (ROI)-based time series of intracortical EEG-source estimates were used instead of pairs of EEG-channel time series for assessment of functional EEG connectivity.

The underlying concept of phase synchronization is that different brain areas are thought to be more connected, directly or via a third source, the higher the non-linear coherence, i.e., phase synchronization, between the two signals is (for a review of the concept, see Fell and Axmacher, 2011). For computation of phase synchronization of EEG signals, the so-called "lagged non-linear connectivity" (Pascual-Marqui et al., 2011) measure was used. It is independent of the signal amplitude and strictly relies on the synchronization of phases. According to previous topographical EEG studies (Fingelkurts et al., 2007; Leuchter et al., 2012), it was hypothesized that patients with MDD would reveal increased connectivity between the SGPFC and the DLPFC or the MPFC within the delta, theta, alpha and beta frequency range.

In addition, we explored the changes of the connectivity measure in a subgroup of MDD patients after 2 weeks of antidepressant treatment compared with findings in HC after the same retest interval. An exploratory analysis analyzed the association between the connectivity measure and scores on the Hamilton depression rating scale (HDRS) and their changes over time.

2. Methods

2.1. Patients and controls

The study was approved by the local ethics committee. Written informed consent was obtained before the study began according to the Declaration of Helsinki. The study group comprised 60 patients (Table 1) with a current DSM-IV diagnosis of major depressive disorder (MDD). All patients were recruited from inpatients and outpatients admitted to the Psychiatric Department at the University Hospital of Leipzig between 2007 and 2011. Diagnosis of MDD was determined for each patient after clinical evaluation by a senior physician; patients were included if they scored at least 11 points on the 21-item HDRS (Hamilton, 1960). Exclusion criteria for patients were a clinically significant neurological or other medical disorder, the use of centrally active medications in the last 4 weeks or a co-morbid DSM-IV axis I disorder. From 173 patients who were initially screened, 60 patients were identified as meeting all inclusion criteria. All patients were scheduled for a routine EEG examination shortly after admission. On the same day, a baseline HDRS score was established by an experienced clinician. For 30 patients, there was a second HDRS assessment 2 weeks after they started medication with escitalopram or mirtazapine (see Table 1), following an in-house protocol for treatment of MDD. A second EEG recording was carried out in 21 patients.

The control group consisted of 60 healthy subjects that were age- and sex-matched to the MDD group (see Table 1) and free of psychopharmacological medication. Their data were drawn from the database of the Department of Psychiatry of the University Leipzig, recorded from 2008 to 2011. Controls who met the criteria of DSM-IV axis I disorders as determined by the Structured Clinical Interview for DSM-IV (SCID-I; Wittchen, 1994) or who had a history or actual symptoms of neurological disorders that required treatment were not included. Two weeks after the baseline EEG, 23 healthy controls were scheduled for a second EEG recording.

2.2. EEG recording and artefact correction

Resting EEG was recorded between 9 a.m. and 3 p.m. The participants were seated in a half-reclining position, light was approximately 40 lx, and the room was sound-attenuated. The average temperature was maintained at 20–23 °C. Fifteen minutes of resting EEG were recorded under eyes closed conditions with a 40-channel QuickAmp amplifier (*Brain Products GmbH*; Gilching, Germany) and 31 electrode sites (Ag/AgCl electrodes) according to an extended international 10–20 system (Fp1, Fp2, F3, F4, F7, F8, Fz, FC1, FC2, FC5, FC6, C3, C4, T7, T8, Cz, CP5, CP6, TP9, TP10, P3, P4, P7, P8, Pz, O1, O2, PO9, PO10, T1, T2) at a sampling rate of 1 kHz, referenced against common average. Impedances were kept below 10 kΩ and electro-oculogram (EOG) electrodes were placed above the left eye and below the right eye. EEG data were preprocessed using BrainVision Analyzer 2.0 software (*BrainProducts*; Gilching, Germany). EEG raw data were filtered at 70 Hz (low-pass), 0.5 Hz (high-pass) and 50 Hz (notch-filter, range 5 Hz). EEG time series then were segmented into consecutive 2-s intervals. Simultaneous video-recordings were used to screen each segment for open eyes and to exclude these segments. Eye-movement artefacts were removed by extracting 1 to 3 out of 31 independent components (IC; using Infomax algorithm, Vision Analyzer 2.01, Gilching, Germany)

Table 2
Depicted are *T*-values of *T*-test comparisons of functional connectivity from the subgenual prefrontal cortex (SGPFC) to the right (r) and left (l) medial prefrontal cortex (MPFC) and dorsolateral prefrontal cortex (DLPFC) for 60 patients (MDD) and 60 matched healthy controls (HC).

	MDD ($n=60$) vs HC ($n=60$) df 118	SGPFC-rDLPFC	SGPFC-lDLPFC	SGPFC-rMPFC	SGPFC-lMPFC
Delta	*MDD (Mean/SD)*	0.04/0.054	0.029/0.028	0.032/0.039	0.034/0.047
	HC (Mean/SD)	0.020/0.019	0.024/0.024	0.021/0.021	0.021/0.022
	T-value	2.79	1.13	1.93	1.95
	p-value	0.006	0.26	0.06	0.05
Theta	*MDD (Mean/SD)*	0.020/0.020	0.021/.020	0.023/0.027	0.021/0.020
	HC (Mean/SD)	0.019/0.016	0.019/0.016	0.018/0.014	0.016/0.011
	T-value	0.47	0.69	1.20	1.76
	p-value	0.64	0.49	0.23	0.08
Alpha	*MDD (Mean/SD)*	0.048/0.045	0.052/0.047	0.046/0.049	0.042/0.037
	HC (Mean/SD)	0.035/0.030	0.026/0.024	0.030/0.027	0.022/0.017
	T-value	1.83	3.86	2.29	3.71
	p-value	0.07	**0.0002** **	0.02	**0.003***
Beta	*MDD (Mean/SD)*	0.010/0.008	0.012/0.011	0.010/0.009	0.009/0.010
	HC (Mean/SD)	0.011/0.012	0.010/0.008	0.011/0.013	0.011/0.012
	T-value	0.86	−0.51	−0.33	−0.69
	p-value	0.4	0.61	0.73	0.49

($p<0.05$ after correction for multiple comparison is marked by "*", $p<0.01$ by "**"; *df*=degree of freedom; SD=standard deviation).

that clearly represented vertical and horizontal eye movements and had been identified by visual (topographic) inspection of the independent component analysis (ICA) maps and comparisons with the EEG and EOG time series (Delorme et al., 2007; Olbrich et al., 2011). Due to the influence of ICA correction on coherence measures (Castellanos and Makarov, 2006), only ICs without visible neural activity were discarded. Any segment that still contained muscle, movement, sweating or eye-movement artefacts, as revealed by a visual inspection by two experienced clinical raters, was excluded from further analysis (no subject had more than 15% artefacts). On one side the EEG was segmented into no less than 2-s epochs to achieve a sufficient frequency resolution of 0.5-Hz steps for assessment of the different EEGbands, and on the other side into no longer segments to obtain a high number of epochs to increase the validity of the connectivity measure. These 2-s EEG epochs were exported for further analysis.

2.3. Regions of interest (ROIs)

ROIs were defined using seed points with inclusion of all grey matter voxels within a radius of 10 mm. The initial solution space in eLORETA consisted of 6239 grey matter voxels. One ROI was assigned for the left (18 voxels) and for the right (20 voxels) DLPFC, and for the left (7 voxels) and right (5 voxels) MPFC. Because of the restricted spatial resolution of the eLORETA approach, the left and right SGPFC were defined in one single ROI (16 voxels). The Montreal Neurological Institute (MNI) coordinates for the right/left DLPFC were $x=30/-30$, $y=35$, $z=40$; for the right/left MPFC, $x=15/-15$, $y=62$, $z=10$, and for the SGPFC, $x=0$, $y=30$, $z=-6$. The ROIs were chosen according to previously identified regions of altered metabolic function or anatomical structure in MDD (Drevets et al., 1997; Pizzagalli, 2011; Davey et al., 2012; Fox et al., 2012a). For statistical analysis, time series with the average current density of all voxels from one ROI were calculated before computing connectivity between the ROIs.

2.4. Connectivity measure and eLORETA

EEG connectivity analysis has been performed using the exact low resolution electromagnetic tomography (eLORETA) software (Roberto Pascual-Marqui/The KEY Institute for Brain-Mind Research University Hospital of Psychiatry, Zurich). The eLORETA algorithm is a linear inverse solution for EEG signals that has no localization error to point sources under ideal (noise-free) conditions (Pascual-Marqui et al., 2002). Studies that used EEG with an even lower number of electrode sites than used in this study in conjunction with simultaneously recordings in other neuroimaging modalities cross-validated the LORETA algorithm and showed overlapping results of intracortical EEG-source estimates and, for exampole, the BOLD signal (Mulert et al., 2004; 27 electrodes) or glucose metabolic rate (Pizzagalli et al., 2004; 28 electrodes).

Connectivity between two regions was defined as the non-linear dependence, i.e., phase synchronization, of intracortical EEG-source estimates as this measure has been used for, for example, detection of long range coherence of gamma oscillations in schizophrenia (Mulert et al., 2011) and increased functional connectivity in schizophrenia-like episodes in epileptic patients (Canuet et al., 2011). Phase synchronization measures the similarity of two time series by means of the phases of the analyzed signal; its value has no unit and ranges from 0, indicating no synchronization, to 1, indicating the highest possible synchronization. It was calculated for the EEG delta (0.5–3.5 Hz), theta (4–7.5 Hz), alpha (8–12 Hz) and beta (12.5–20 Hz) frequency bands. This method of calculating the phase synchronization between time series did not rely on any amplitude information. Instead, absolute values of the complex valued (Hermitian) coherency between the normalized Fourier transforms were calculated. Since zero-lag-phase synchronization can be found due to non-physiological effects such as volume conduction, only lagged phase synchronization was used while the instantaneous zero-lag-phase contribution was not considered. Detailed descriptions of the method and related equations can be found in Pascual-Marqui (2007).

2.5. Statistics

Statistical analysis was performed using eLORETA (Pascual-Marqui, 2002) and STATA software (Stata Statistical Software: Release 11, College Station, TX). Phase synchronization of the four EEG frequency bands (delta, theta, alpha and beta) was compared using two-tailed *t*-tests with Bonferroni correction for multiple testing, i.e., for the collection of tests performed for all possible connections between ROIs and number of frequency bands.

To study the effects of medication after 2 weeks of treatment as well as the stability of the connectivity measure after 2 weeks in HCs, a repeated-measures analysis of variance (ANOVA) was performed with "group" (MDD vs. HC) as the between-subject factor, "time" (baseline and after 2 weeks) as the within-subject factor, and connectivity measures as the dependent variables. Corrections of degrees of freedom due to violations of the independence of observations in a repeated measures design were applied. Post hoc tests for each connection were performed using the Scheffé test.

To learn more about the association between the phase synchronization and symptom severity, an exploratory analysis was performed with calculation of Pearson correlation coefficients for correlations between baseline HDRS total scores and the EEG phase-synchronization measure at each frequency range. Additionally, correlation analyses were performed for the relative change of HDRS scores after 2 weeks of treatment and the baseline connectivity measures as well as for the correlation between changes of HDRS scores and changes of connectivity measures after 2 weeks.

EEG-connectivity measures are affected by to preprocessing steps like ICA-artefact minimization (Castellanos and Makarov, 2006) and differences in the signal-to-noise ratio (SNR) between groups. To exclude a possible impact of the applied preprocessing transformations on the results, the amount of variance of all independent components that had been excluded was calculated for each group and compared using a two-sided *t*-test. Further, the SNR after preprocessing was calculated for each electrode over all available non-artefact segments and compared between patients with MDD and HCs using a two-sided *t*-test.

3. Results

3.1. Sociodemographic variables and data quality

No age or sex differences were found between patients and HC (see Table 1). Also, there were no differences between the subsample of antidepressant-treated patients and HC (see Table 1 for details), and both patients and controls were compared in a second EEG performed after 14 days.

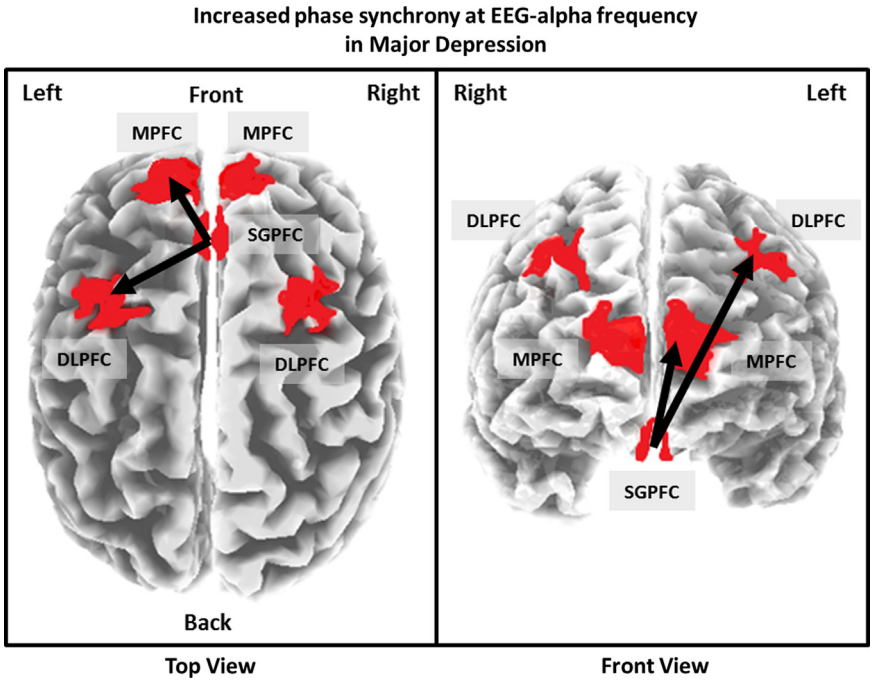

Fig. 1. Visualized increased functional connectivity between the subgenual prefrontal cortex (SGPFC) and the left medial prefrontal cortex (MPFC) and between the SGPFC and the left dorsolateral prefrontal cortex (DLPFC). Black arrows indicate significantly increased phase synchronization for 60 unmedicated patients suffering from major depression (MDD) at the EEG alpha frequency in comparison to 60 healthy controls (HC) after correction for multiple comparisons.

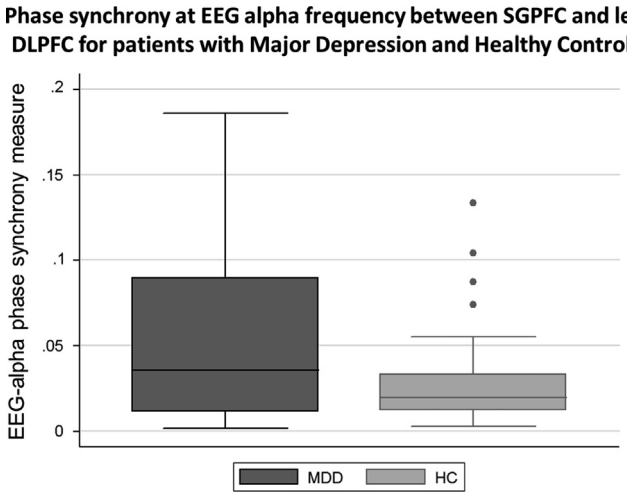

Fig. 2. Boxplots of the connectivity strength between the subgenual prefrontal cortex (SGPFC) and the left dorsolateral prefrontal cortex (DLPFC) at the alpha frequency range for 60 unmedicated patients with MDD and 60 healthy controls (HC). Lines in boxes show median values, boxes indicate 25th and 75th percentile, whiskers show upper and lower adjacent values and dots show outliers.

Concerning the analysed EEG data, out of 450 2-s segments from the resting period, in average 421.6 segments (SD 22.0) for patients with MDD and 424.6 segments (SD 11.5) for HC entered the analysis after removal of artefacts (MDD average 28.4, SD 5.3; HC average 25.4, SD 2.8). There was no significant difference in the amount of artefact segments that had been removed (two-tailed *t*-test; $p=0.36$). No difference was found when the explained variance of excluded independent components was compared between groups (MDD average variance 28.6%, SD 19.7%; HC average variance 22.2%, SD 13.3%; two-tailed *t*-test; $p=0.14$). Also, no statistical difference was found for the SNR at any of the 31 included channels between the MDD patients and the HCs (HC SNR 0.52–0.65; SD 0.39–0.48; MDD SNR 0.60–0.86; SD 0.33–0.66; $p>0.14$). This suggests that ICA-artefact correction did not account for differences between groups.

3.2. Altered connectivity in MDD patients

Analysis of differences of connectivity measures between the patients with MDD and the HCs revealed a significantly increased connectivity at the alpha frequency range between the SGPFC and the left DLPFC (see Table 2, Figs. 1 and 2), between the SGPFC and the left MPFC (see Table 2 and Fig. 1) and between the SGPFC and the right MPFC (see Table 2). Only the increased connectivity between the SGPFC and the left DLPFC and the left MPFC remained significant after Bonferroni correction for multiple comparisons. No significant differences of connectivity measures were found for the delta, theta, or beta frequency band.

3.3. Changes of connectivity after treatment

The repeated measures ANOVA (MDD: $n=21$; HC: $n=23$) revealed a significant effect for the "time × group" interaction for connectivity between the SGPFC and the right DLPFC at the beta frequency band (see Table 3; Fig. 3, left). For the factor "time", repeated measures ANOVA showed a significant increase of connectivity between the SGPFC and the right DLPFC for patients with MDD at the beta frequency range after 2 weeks of treatment in comparison to baseline measurement (see Table 3; Fig. 3, left). No significant effects of the factor "time" were found for HC.

Post-hoc analysis revealed a significant difference between groups at the baseline measurement for connectivity between the SGPFC and the left MPFC at the alpha frequency with increased phase synchronization measure for the MDD group (Scheffé test with $F=8.16$, $p<0.01$; see Fig. 3, right). After 2 weeks, post-hoc analysis again revealed a significantly increased connectivity for MDD between the SGPFC and the left MPFC (Scheffé test with $F=4.61$, $p<0.04$) at the alpha frequency (see Fig. 3, right). Additionally, increased connectivity for MDD in comparison to HC was found after 2 weeks of treatment within the beta

Table 3
Repeated measures analysis of variance (rANOVA) for comparison of baseline connectivity measures and retest after two weeks (with antidepressant treatment in patients with major depressive disorder—MDD) from the subgenual prefrontal cortex (SGPFC) to the right (r)/ left (l) dorsolateral prefrontal cortex (DLPFC) and the medial prefrontal cortex (MPFC). While factor "time" had no effect in the healthy control (HC) group, connectivity at the beta frequency increased for the MDD group between the SGPFC and the right DLPFC.

		time MDD ($n=21$)				time HC ($n=23$)				time × group (MDD=21; HC=23)			
		SGPFC-rDLPFC	SGPFC-lDLPFC	SGPFC-rMPFC	SGPFC-lMPFC	SGPFC-rDLPFC	SGPFC-lDLPFC	SGPFC-rMPFC	SGPFC-lMPFC	SGPFC-rDLPFC	SGPFC-lDLPFC	SGPFC-rMPFC	SGPFC-lMPFC
Delta	*Baseline (Mean/SD)*	0.021/ 0.025	0.022/ 0.026	0.028/ 0.041	0.023/ 0.024	0.018/ 0.015	0.020/ 0.017	0.018/ 0.012	0.015/ 0.010				
	Retest (Mean/SD)	0.025/ 0.041	0.021/ 0.041	0.027/ 0.045	0.019/ 0.021	0.017/ 0.013	0.017/ 0.012	0.018/ 0.014	0.016/ 0.011				
	F-value	0.42	0.07	0.08	0.97	0.15	1.01	0.05	0.34	0.60	0.06	0.13	1.38
	p-value	0.52	0.79	0.78	0.34	0.70	0.35	0.82	0.56	0.44	0.80	0.72	0.25
Theta	*Baseline (Mean/SD)*	0.021/ 0.025	0.022/ 0.026	0.028/ 0.041	0.023/ 0.024	0.018/ 0.015	0.020/ 0.017	0.018/ 0.012	0.015/ 0.010				
	Retest (Mean/SD)	0.025/ 0.041	0.021/ 0.041	0.027/ 0.045	0.019/ 0.021	0.017/ 0.013	0.017/ 0.012	0.018/ 0.014	0.016/ 0.011				
	F-value	0.42	0.07	0.08	0.97	0.15	1.01	0.05	0.34	0.6	0.06	0.13	1.38
	p-value	0.52	0.79	0.78	0.34	0.7	0.33	0.82	0.56	0.44	0.8	0.72	0.25
Alpha	*Baseline (Mean/SD)*	0.056/ 0.049	0.052/ 0.049	0.052/ 0.048	0.046/ 0.035	0.033/ 0.037	0.028/ 0.031	0.029/ 0.030	0.022/ 0.020				
	Retest (Mean/SD)	0.064/ 0.078	0.059/ 0.063	0.066/ 0.066	0.046/ 0.045	0.033/ 0.033	0.023/ 0.020	0.032/ 0.030	0.024/ 0.020				
	F-value	0.4	0.34	0.92	0	0	2.17	0.15	0.34	0.34	0.95	0.58	0.05
	p-value	0.54	0.57	0.35	0.99	0.99	0.16	0.71	0.57	0.56	0.33	0.45	0.83
Beta	*Baseline (Mean/SD)*	0.008/ 0.004	0.011/ 0.010	0.012/ 0.012	0.011/ 0.014	0.012/ 0.016	0.010/ 0.008	0.012/ 0.017	0.012/ 0.012				
	Retest (Mean/SD)	0.017/ 0.015	0.012/ 0.014	0.018/ 0.018	0.014/ 0.012	0.009/ 0.007	0.008/ 0.005	0.011/ 0.008	0.009/ 0.006				
	F-value	7.23	0.34	3.52	0.81	0.91	0.84	0.05	1.52	6.78	1.10	2.11	2.22
	p-value	**0.01***	0.56	0.08	0.38	0.35	0.37	0.83	0.23	**0.01***	0.32	0.15	0.14

(Significant findings are marked by "*"; SD=standard deviation).

frequency range between the SGPFC and the right DLPFC (Scheffé test with $F=5.90$, $p<0.02$; see Fig. 3, left).

3.4. Correlation between connectivity measures and HDRS scores

Correlation analysis between HDRS scores and connectivity measures at baseline revealed a tendency for a weak positive correlation ($r=0.22$; $p<0.09$, see Table 4) for connectivity between the SGPFC and the left DLPFC at the alpha frequency. No association was found at other frequency bands. Since the MDD sample included patients with relatively low HDRS scores, correlation analysis was performed for patients with an HDRS score ≥ 16. Again, the highest correlation was found for connectivity between the SGPFC and the left DLPFC at the alpha band ($r=0.22$, see Table 4), but it remained non-significant ($p=0.13$).

To assess the value of the connectivity measure for treatment prediction, the correlation between the relative change of HDRS scores in percentage after 2 weeks of treatment and the connectivity measures at baseline for the MDD subgroup ($n=30$) was computed and revealed a weak positive correlation for measures between the SGPFC and the right MFC at the beta frequency range ($r=0.36$, $p=0.05$; see Table 4). For patients with an HDRS score ≥ 16, the same baseline connectivity yielded the highest (but non-significant) correlation ($r=0.31$, $p=0.12$; see Table 4).

To study the association between improvement of depressive symptoms and change of connectivity, the correlation between the change of HDRS score and the change of phase synchronization from baseline to retest was computed. An increase of theta band connectivity between the SGPFC and the right and left DLPFC and an increase of alpha band connectivity between the SGPFC and the left MPFC correlated significantly with reduction of HDRS scores (see Table 4) for the whole patient retest group. Within the subgroup with a HDRS score ≥ 16, a significant correlation was found between the HDRS reduction and increases in alpha connectivity between the SGPFC and the left DLPFC and for increases in beta connectivity between the SGPFC and the right DLPFC (see Table 4 and Fig. 4).

In an exploratory analysis, changes of connectivity between responders (patients with HDRS scores ≥ 16 at baseline; change of HDRS after 2 weeks $>30\%$; $n=6$) and non-responders ($n=5$) were compared. As the only significant results, responders showed a larger increase in beta connectivity between the SGPFC and the DLPFC (two-tailed t-test, $p<0.03$).

4. Discussion

The results show an increased functional connectivity by means of EEG lagged phase synchronization during rest between the subgenual prefrontal cortex and the left dorsolateral prefrontal cortex and the left medial prefrontal cortex within the EEG alpha frequency band in MDD in comparison to findings in healthy controls. In an EEG retest of a subgroup of HC after 2 weeks, the phase synchronization did not show any significant changes, providing evidence for the retest stability of the measure. In contrast, within the subgroup of MDD patients that underwent retest after 2 weeks of antidepressant medication, an increase of phase synchronization was found for the EEG beta frequency band. Baseline beta phase synchronization also correlated with the change of HDRS score after 2 weeks, thus being a possible predictive marker.

The finding of an increased EEG alpha frequency phase synchronization at baseline is in line with results from Leuchter et al. (2012), who found a significant increase of EEG-based coherence for the EEG alpha range between frontopolar and temporal regions in a topographic EEG study in MDD. Due to the dependency of topographic coherence measures on the chosen montage (Hu et al., 2010) in channel or "hubnode"-wise analysis, the results of the presented study extend the findings of Leuchter et al. since

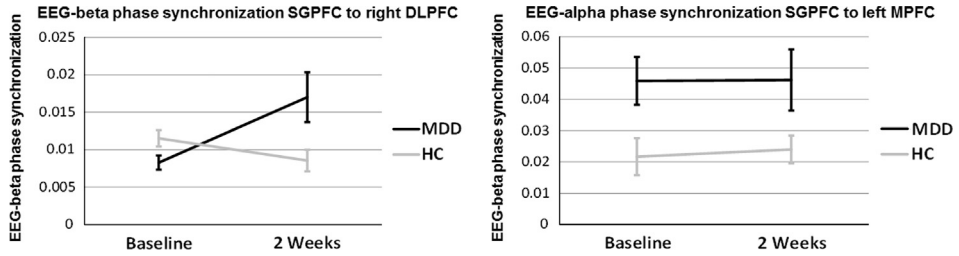

Fig. 3. Results of repeated measures ANOVA of the connectivity measure for 21 patients with major depression (MDD) from baseline to 2 weeks after antidepressant medication and for 23 healthy controls (HC) at baseline and at retest 2 weeks later. Shown are results for connectivity between the subgenual prefrontal cortex (SGPFC) and the right dorsolateral prefrontal cortex (DLPFC) at the EEG beta frequency with no differences at baseline and an significant increase only for the MDD group two weeks later (left). Connectivity between the SGPFC and the left medial prefrontal cortex (MPFC) for the EEG alpha band is increased for patients at baseline as well as after 2 weeks of treatment in comparison to HC (right). Whiskers show standard errors.

Table 4
Pearson correlation coefficients of the association between the Hamilton depression rating scale (HDRS) and phase synchronization for connections from the subgenual prefrontal cortex (SGPFC) to the right (r) and left (l) medial prefrontal cortex (MPFC) and dorsolateral prefrontal cortex (DLPFC). Left panel shows patients with a HDRS > 11; right panel shows patients with HDRS > =16.

n=60	Delta	Theta	Alpha	Beta	*n=44*	Delta	Theta	Alpha	Beta
Correlation between baseline HDRS and baseline connectivity									
SGPFC-rDLPFC	−0.2	0.01	0.19	0.14	(*Baseline HDRS > =16*)	−0.1	−0.05	0.13	−0.05
SGPFC-lDLPFC	−0.12	−0.02	**0.22**°	0.07		−0.13	−0.16	0.24	−0.08
SGPFC-rMPFC	−0.14	0.05	−0.08	0.05		−0.12	−0.07	−0.18	−0.08
SGPFC-lMPFC	−0.16	−0.02	0.11	−0.01		−0.14	−0.17	0.03	−0.1
n=30	Delta	Theta	Alpha	Beta	*n=20*	Delta	Theta	Alpha	Beta
Correlation between change of HDRS and baseline connectivity									
SGPFC-rDLPFC	−0.07	0.15	0.16	0.26	(*Baseline HDRS > =16*)	−0.11	0.17	0.18	0.27
SGPFC-lDLPFC	−0.15	0.12	0.07	0.25		−0.22	0.13	0.01	0.23
SGPFC-rMPFC	−0.06	0.23	0.03	**0.36***		−0.09	0.24	0.13	0.31
SGPFC-lMPFC	−0.03	0.13	0.02	0.1		−0.05	0.11	−0.03	0
n=21	Delta	Theta	Alpha	Beta	*n=11*	Delta	Theta	Alpha	Beta
Correlation between change of HDRS and change of connectivity									
SGPFC-rDLPFC	0.2	**0.48***	0.36	0.21	(*Baseline HDRS > =16*)	0.49	0.49	0.4	**0.67***
SGPFC-lDLPFC	0.11	**0.48***	0.33	0.15		0.53	0.53	**0.62***	0.45
SGPFC-rMPFC	0.17	**0.38**°	0.4	0.14		0.4	0.4	0.34	0.2
SGPFC-lMPFC	0.26	0.34	**0.52***	0.24		0.38	0.38	**0.6**°	0.4

($p = < 0.10$ is marked by "°", $p < 0.05$ by "*").

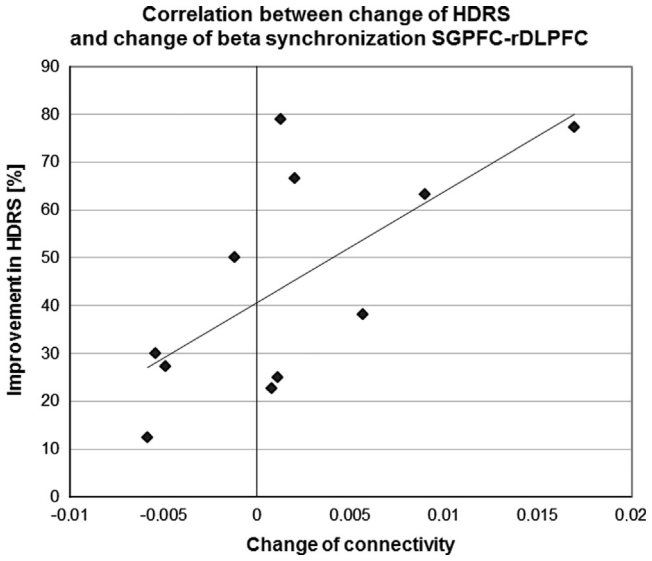

Fig. 4. Correlation (Pearson correlation coefficient, $r=0.67$, $p < 0.05$) between the change of Hamilton depression rating scale (HDRS) score and change of beta phase synchronization between the subgenual prefrontal cortex (SGPFC) and the right dorsolateral prefrontal cortex (rDLPFC) in 11 patients with major depressive disorder and an initial HDRS score ≥ 16 after 2 weeks of medication.

the phase-synchronization measure was computed for intracortical EEG-source estimates that are independent of EEG montages. Altered connectivity could thus be traced down to different intracortical areas by using the ROI-based eLORETA approach.

EEG alpha activity is seen as the marker of the idling brain that reflects the intrinsic activity of neuronal assemblies that are disengaged from environmental inputs and driven by pacemaker neurons in the thalamus (Steriade et al., 1993). Makeig et al. (2002) reported that responses to incoming stimuli vary as a function of phase of the basal brain rhythm, i.e., EEG alpha activity. An increase of phase synchronization at the EEG alpha rhythm between distant brain areas in MDD might thus be interpreted as a lack of local phase resetting, probably due to disturbed processing of external or internally generated inputs. Hence, in MDD, the alpha rhythm and its phase (which are driven by thalamic pacemakers on cortical areas) could be less affected by local cortical processing, resulting in the measurement of increased phase synchronization. In this light, an increase of phase synchronization in the alpha frequency in MDD might not reflect an increase of direct connectivity between brain areas within the PFC that are relevant for, e.g., emotional processing but could be a sign of locally disturbed cortical processing of input patterns and altered thalamocortical loops (Llinás et al., 1999).

However, on one side, baseline EEG alpha connectivity showed a weak correlation with symptom severity and high baseline beta

connectivity predicted treatment response. On the other side, further increases of alpha and beta connectivity from baseline to retest correlated with symptom reduction. This suggests that altered phase synchronization might not reflect pathological neuronal activity itself but could be a sign of a cortical counter-reaction to depressed mood and affective dysregulation. As Isaac and Bayley (2012) discuss, it is questionable whether changed connectivity patterns between the SGPFC and the DLPFC are a cause or a consequence of affective dysregulation. If one considers the latter, during treatment the reduction of symptoms might be achieved through enhancement of this counter-mechanism of the brain by improving, e.g., alpha- and beta-band-dependent processing of emotional and cognitive content (Ray and Cole, 1985). This view is supported by EEG-coherence studies in healthy subjects that found altered connectivity, especially within the beta band, during presentation of emotionally affecting stimuli (e.g., Aftanas et al., 1998; Miskovic and Schmidt, 2010). It has been suggested that increased beta connectivity mediates a top-down control mechanism for affective regulation while a decrease might lead to diminished control of emotional processing (Reiser et al., 2012). In this light, the increase of beta-phase synchronization after treatment in the presented study might also reflect a medication-mediated gain of control over affective engagement. Saletu et al. (1992, 2010) demonstrated that antidepressant drugs modulate properties of EEG beta activity even after a single oral administration. Still, the presented retest results and their support for EEG-connectivity measures being a feasible biomarker for treatment in MDD have to be interpreted with caution due to the relatively small sample size and the short 2-week retest interval.

In contrast to previous studies (e.g., Fingelkurts et al., 2007; Lee et al., 2011; Leuchter et al., 2012), only the EEG alpha frequency range showed significant differences of phase synchronization in MDD in contrast to HC at baseline in the presented data. While Fingelkurts et al. (2007) reported an increase of alpha and theta functional connectivity in patients and Leuchter et al. (2012) found increases in alpha, beta, delta and theta connectivity. Further, Lee et al. (2011) reported a negative association between coherent delta/theta power fluctuations and treatment response, while within our study symptom reduction correlated with beta band phase synchronization. These differences can be explained in part by differences in the connectivity measures used: While Lee et al. and Leuchter et al. used a coherence measure that is not totally independent of amplitude, the phase-synchronization measure used in the present study did not rely on any amplitude information. Fingelkurts et al. (2007) and also Lee et al. (2011) used a measure that calculated connectivity based on power rather than phase synchronization. Therefore, their results reflect different aspects of neuronal interaction. Further, we strictly used a lagged phase synchronization measure to exclude volume-conduction effects (Pascual-Marqui, 2007) that might have affected the results. These methodological differences need to be examined further if reliable biomarkers and standards are to be established for assessment and analysis of EEG recordings (Jobert et al., 2012).

At the neurotransmitter level, a potential explanation for altered phase synchronization comes from the recently developed hypothesis that gamma-aminobutyric acid (GABA) as the leading inhibitory neurotransmitter and glutamate as the main excitatory cortical neurotramsmitter play a crucial role in the pathomechanisms of MDD. From animal and clinical studies (for review, see Brambilla et al., 2003) as well as from magnetic resonance spectroscopy (MRS) studies, there is evidence of decreased levels of GABA and glutamate in MDD within several cortical structures including the DLPFC and the anterior cingulate cortex (Hasler et al., 2007; Bhagwagar et al., 2008; Luscher et al., 2011). Several lines of evidence point to the influence of inhibitory GABA and excitatory glutamate neurotransmission on the synchronization of neural activity (Steriade et al., 1993; Llinás et al., 2005; Gonzalez-Burgos and Lewis, 2008; Panuccio et al., 2009); hence, an imbalance or altered levels of GABA and glutamate may lead to the observed alterations of EEG-phase synchronization. Via a disturbed GABAergic or glutamatergic neurotransmission, decreased volumes of prefrontal areas in MDD, mainly reflecting decreased amounts of glial cells which are involved in the metabolic cycles of these transmitters (Öngür et al., 1998; Cotter et al., 2002), could be linked to alterations of functional connectivity as reported in this study. The fact that even recovered patients with MDD were found to have decreased levels of GABA (Bhagwagar et al., 2008) might reflect the missing change-of-phase synchronization in the alpha band after 2 weeks of treatment in MDD.

There is further evidence from animal studies of the influence of other neurotransmitter systems such as noradrenaline and serotonin (e.g., Dzirasa et al., 2010; Schweimer et al., 2011) on phase synchronization of neuronal activity. However, discussing these findings is beyond the scope of this work. To disentangle the complex relationship of the different frequency bands and their synchronization throughout different brain areas by taking into account the role of possibly involved neurotransmitters, studies that simultaneously assess EEG and neurotransmitter levels are required.

The presented findings extend the reported altered structural connectivity (Kwaasteniet et al., 2013) and increased functional MRT-based connectivity in frontal areas in MDD (Greicius et al., 2007; Davey et al., 2012). The functional connectivity between areas of the left DLPFC (which is associated with a high clinical efficacy as a target in TMS treatment) and the SGPFC shows the opposite pattern with a negative correlation of BOLD signals (Fox et al., 2012a). However, while the BOLD signal is a surrogate marker of neuronal activity, the EEG provides direct evidence for altered neuronal interaction between frontal brain sites that are involved in emotional regulation. An increase of coherent BOLD signals between, for example, the SGPFC and other prefrontal areas and the shown increase of phase synchronization in MDD have been interpreted as complementary markers of altered CNS activity (Leuchter et al., 2012). While fMRI-based connectivity measures have been shown to be stable over time in healthy subjects (Fox et al., 2012b), the finding of unchanged EEG-connectivity measures in the subgroup of HC after 2 weeks in our study provides the first evidence of the state character of the electrophysiological measure, although longer retest intervals are needed for further validation. While in fMRI studies, correlations between altered connectivity and clinical characteristics have been reported (Wang et al., 2013), within our study only a tendency for a positive correlation between alpha band phase synchronization and HDRS scores was found. Still, the positive correlation of EEG beta phase synchronization and the change of HRDS score after 2 weeks of treatment paralleled the increases of theta and alpha connectivity found in the whole study group, as well as the increases of beta and alpha connectivity in a more severely depressed subgroup. Further, responders to antidepressants were differentiated from non-responders by a larger increase of beta connectivity after treatment. These findings are a first hint of the potential predictive value of phase-synchronization alterations and their association with treatment-related changes in neurophysiological activity. However, larger cohorts and longer retest intervals are needed to clarify the predictive power and relation between EEG-based phase synchronization and severity of depression.

Some important limitations of the study should be mentioned: First the EEG-frequency bands have not been adapted to the individual peak frequencies. Since, for example, the individual alpha peak frequency has been shown to be predictive for

treatment outcome in MDD (Arns et al., 2012), an individual peak frequency approach could increase the sensitivity for alterations of phase synchronization especially at the alpha frequency range. Second, the used EEG localization technique eLORETA has a limited spatial resolution and thus might have blurred the connectivity measures to some degree due to the underlying assumption of maximum similarity of neuronal activity between neighboring voxels (Nichols and Holmes, 2002). Further, although we showed that the preprocessing steps using ICA did not contribute to the group differences, it still might be that these preprocessing steps had an influence on the connectivity measure (Castellanos and Makarov, 2006). In the light of findings from other neuroimaging modalities, however, the presented results seem plausible and reliable.

5. Conclusion

The synchronization and desynchronization of neuronal activity as assessed by EEG is one footprint of the working brain. The distributed but coupled rhythmic activity at distinct brain areas during rest represents the steadily ongoing self-organization of neuronal activity that makes the brain distinct from a matrix of random oscillations. MDD is characterized by disturbances of neuronal interaction, especially in prefrontal regions such as the SGPFC and the DLPFC. By bridging electrophysiological findings with results of structural and functional imaging studies, knowledge about the pathogenesis of depression can be improved. Further research should try to incorporate this knowledge for the development of diagnostic tools and markers for treatment prediction.

Financial disclosures

U. Hegerl has been or is participating in advisory boards of Lilly, Wyeth, Lundbeck, and Sanofi-Aventis. He received financial support for an Investigator Initiated Trial from Lundbeck. He received honoraria for single lectures as well as sponsorships for symposia and an Internet service from Cephalon and other pharmaceutical companies, health insurance companies, and other parties. The remaining authors PS, SO, AT and TC report no biomedical financial interests or potential conflicts of interest.

Acknowledgements

We thank Mrs. I. Thomas and Mrs. M. Siebert for their technical assistance.

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