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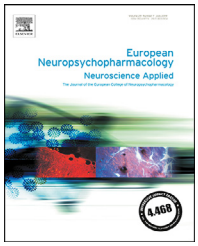

Transdiagnostic modulation of brain networks by electroconvulsive therapy in schizophrenia and major depression

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Abstract
Major depressive disorder (MDD) and schizophrenia (SCZ) share neurobiological and clinical commonalities. Altered functional connectivity of large-scale brain networks has been associated with both disorders. Electroconvulsive therapy (ECT) has proven to be an effective treatment in severe forms of MDD and SCZ. However, the role of ECT on the modulation of the dynamics of brain networks is still unknown. In this study, we used resting state functional magnetic resonance imaging (rs-fMRI) to investigate functional connectivity in 16 pharmacoresistant patients with SCZ or MDD and a matched group of normal controls. Patients were scanned before

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and after right-sided unilateral ECT. Group spatial independent component analysis was carried out with a multiple analysis of covariance (MANCOVA) approach to estimate the effects of ECT treatment on intrinsic components (INs). Functional network connectivity (FNC) was calculated between pairs of INs. Patients had reduced connectivity within a striato-thalamic network in the thalamus as well as increased low frequency oscillations in a striatal network. ECT reduced low frequency oscillations (LFOs) on a striatal network along with increasing functional connectivity in the medial prefrontal cortex within the DMN. Following ECT treatment, the FNC of the executive network was reduced with the DMN and increased with the salience network, respectively. Our findings suggest transnosological effects of ECT on the connectivity of large-scale networks as well as at the level of their interplay. Furthermore, they support a transnosological approach for the investigation not only of the neural correlates of the disease but also of the brain mechanism of treatment of mental disorders.

1. Introduction

The idea that psychiatric conditions are distinct and separate entities with their own symptoms, natural history and treatment has been one on the mainstays of the major nosographic psychiatric systems, including the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2013). Recent views, including the Research Domain Criteria (RDoC) initiative of the National Institutes of Mental Health, fundamentally challenged this idea, proposing that transdiagnostic approaches could better reflect the underlying biology (Insel et al., 2010). Indeed, recent literature has pinpointed common genetic bases for five distinct psychiatric disorders including schizophrenia (SCZ) and major depressive disorder (MDD) (Lee et al., 2013). Convergent results from structural imaging, indicate common volumetric alterations in these disorders (Chang et al., 2018). Furthermore, the clinical presentation of SCZ and MDD frequently overlaps, with depressive symptoms predating of more than 4 years the first admission for SCZ, and being the first clinical changes to appear in these patients (Hafner et al., 2005). On the other hand, almost 30% of young patients with anxiety and depressive disorders can present subthreshold psychotic symptoms (Wigman et al., 2012). Clinical and biological evidence of transnosological commonalities across schizophrenia and MDD has long been acknowledged in treating patients, with an approved use of antipsychotics as adjuvant of antidepressants or in monotherapy for treatment-resistant depression (Zhou et al., 2015) as well as with a controversial use of antidepressants in SCZ (Mao and Zhang, 2015).

Neuroimaging studies in the last decade have suggested that the brain is organized in several intrinsic large-scale networks that span across multiple brain regions and are functionally connected with each other (Smith et al., 2009). Resting state functional magnetic resonance imaging (rs-fMRI) allows the study intrinsic brain networks using functional connectivity, which measures the temporal relationship across spatially remote brain regions that oscillate spontaneously. Alterations of intrinsic functional connectivity in several brain networks have been implicated in both MDD (Sambataro et al., 2017) and in SCZ (Jafri et al., 2008). A very recent meta-analysis on rs-fMRI in SCZ suggested altered functional coupling within and across the executive network (EXE), the salience network (SAL), and default mode network (DMN), as well as in striato-thalamic networks (Dong et al., 2018); another recent rs-fMRI meta-analysis identified alterations in the same networks in MDD (Kaiser et al., 2015). Furthermore, the time courses of the brain networks show also a temporal dependency, independent of spatial proximity, that is called functional network connectivity (FNC). Spontaneous FNC is thought to be crucial for information transfer across remote brain areas and to encode relatedness across segregated neural signals that are eventually processed jointly (Engel et al., 2001). Predictably, altered FNC has been reported in numerous mental disorders, including SCZ (Jafri et al., 2008) and MDD (Sambataro et al., 2017, 2014). SCZ and MDD show also convergent FNC alterations that may reflect common pathophysiological aspects with reduced connectivity of the EXE networks in patients relative to normal controls (NCs) (Wu et al., 2017).

Among other treatment options for treatment-resistant major psychiatric disorders, electroconvulsive therapy (ECT) represents a rapid, safe and effective treatment with an approved use for catatonic SCZ (Lefevre and Bauriaud, 1989; Phutane et al., 2013; Tharyan and Adams, 2005) as well as for suicidal, catatonic, and psychotic MDD (Uk Ect Review Group, 2003). Although a long-standing clinical experience and the incorporation of this technique in the guidelines of treatment of psychiatric disorders, the identification of the neurobiological bases of this neurostimulation procedure remains elusive. In recent years, functional imaging studies have investigated the neural effects of ECT. However, most studies have been focused on the investigation of MDD-specific functional imaging correlates of ECT (see Yrondi et al., 2018, for a review), that suggest a change of functional coupling and neural coherence in the limbic regions as well as in the DMN as neural correlates of ECT (Mulders et al., 2016). Furthermore, ECT has been associated with internetwork connectivity changes between DMN, EXE, dorsal attentional network and SAL (Abbott et al., 2013; Wang et al., 2018). In sharp contrast to the growing neuroimaging literature in MDD, few studies have investigated the neural effects of ECT on SCZ. Increased functional connectivity in midline regions of

Table 1 Demographic and imaging information of the samples.

	MDD	HC^{MDD}	SCZ	HC^{SCZ}	MDD vs HC^{MDD} p-value	SCZ vs HC^{SCZ} p-value	MDD vs SCZ p-value
N	8	10	8	10	-	-	-
gender (F:M)	2:6	3:7	5:3	7:3	0.81	0.73	0.17
Age (years)	43.2 ± 12.2	46.2 ± 10.7	31.12±8.4	32.2 ± 3.7	0.59	0.72	0.04
Education (years)	16.2 ± 5.2	16.2 ± 2.5	14.25 ± 3.5	16.7 ± 2.4	0.98	0.01	0.38
FD (mm)	0.17 ± 0.08	0.14 ± 0.06	0.22 ± 0.09	0.15 ± 0.08	0.37	0.12	0.29
RMS motion (mm)	0.75 ± 0.82	0.26 ± 0.09	0.54 ± 0.48	0.42 ± 0.42	0.08	0.58	0.53
Warping Index	0.85 ± 0.03	0.86 ± 0.03	0.84 ± 0.03	0.85 ± 0.03	0.53	0.53	0.28
N. of ECT sessions	10.5 ± 2.9		12.4 ± 1.8				0.12
HAM-$D_{Pre\text{-}ECT}$	26.6 ± 7.6						
PANSS General$_{Pre\text{-}ECT}$			77.5 ± 5.6				
PANSS Positive$_{Pre\text{-}ECT}$			19.7 ± 13.9				
PANSS Negative$_{Pre\text{-}ECT}$			20.6 ± 5.8				
PANSS Total$_{Pre\text{-}ECT}$			38 ± 11.7				
HAM-$D_{Post\text{-}ECT}$	3.9 ± 2.9						
PANSS General$_{Post\text{-}ECT}$			47 ± 25.0				
PANSS Positive$_{Post\text{-}ECT}$			13.9 ± 4.7				
PANSS Negative$_{Post\text{-}ECT}$			18.6 ± 13.3				
PANSS Total$_{Post\text{-}ECT}$			23.5 ± 10.9				

MDD, Major Depressive Disorder; SCZ, Schizophrenia; HC, Healthy Controls; RMS, Root Mean Squared Difference; FD, framewise displacement; HAM-D, Hamilton Depression Rating Scale; PANSS, Positive and Negative Syndrome Scale; HC^{MDD}, HC matched with MDD; HC^{SCZ}, HC matched with SCZ. P-values of group differences were calculated using two sample t-tests for continuous variables and chi-square tests for gender ratio.

the DMN following ECT was found in these patients, as suggested by recent reports (Huang et al., 2017; Li et al., 2017; Thomann et al., 2017). A study conducted by Thomann and colleagues previously investigated the effects of the ECT on the limbic system of patients with SCZ and MDD. They found increased amygdalar gray matter volume as well reduced functional connectivity of this system (i.e., amygdala) with regions of the SAL, EXE and DMN (Thomann et al., 2017), thus suggesting that regions other than the limbic system may be implicated in ECT response in both disorders. However, the effects of ECT on intrinsic brain networks that are shared in MDD and SCZ remain still unknown.

The aim of this study was to identify a common neural mechanism through which ECT can modulate large-scale brain networks dynamics in MDD and SCZ. Based on previous evidence on the role of brain networks in the pathophysiology of both these disorders as well as on their importance in mediating treatment response, we hypothesized that within-network connectivity in the DMN as well as in the striatal networks, and between-network connectivity in those networks regulating goal-directed behavior would be modulated by ECT treatment in MDD and SCZ.

2. Experimental procedures

2.1. Participants

Sixteen patients ($N = 8$ MDD and $N = 8$ SCZ) and 20 NCs without any psychiatric, neurologic, or medical illness (all Caucasians) participated in the study (Table 1). All participants were right-handed (Oldfield, 1971) and had normal or corrected-to-normal vision. Patients with MDD were significantly older ($p = 0.04$), and did not differ for any other demographic or preprocessing imaging variable when compared with patients with SCZ (two sample t-tests, see Table 1 for details). NCs were matched for age, gender and education with each patient subsample ($N = 10$ for MDD, $N = 10$ for SCZ). Exclusion criteria included age >55 years, past history or presence of any medical or neurological disorder, presence of drug or alcohol abuse, active drug use in the past year, past head trauma with loss of consciousness. The clinical assessment was performed within one day from each MRI scan, within 5 days prior to the first ECT session (baseline), and 6-8 days after the last stimulation. All patients met DSM-IV criteria for SCZ or for MDD as assessed with clinical interview by trained psychiatrists. Symptom severity was assessed with the 17-items version of the Hamilton Depression Rating Scale (HAM-D, Hamilton, 1967) for patients with MDD ($HAM\text{-}D_{Pre\text{-}ECT} = 26.6 \pm 7.6$; $HAM\text{-}D_{Post\text{-}ECT} = 3.9 \pm 2.9$; Mean± Standard deviation), and with the Positive and Negative Syndrome Scale (PANSS, Kay et al., 1987) for patients with SCZ ($PANSS\ Total_{Pre\text{-}ECT} = 38 \pm 11.7$; $PANSS\ Total_{Post\text{-}ECT} = 23.5 \pm 10.9$; Mean± Standard deviation), respectively. Patients were ECT-naïve and were included only if their drug treatment (see supplementary Table S.2, S.3 for details) was stable for at least two weeks before the baseline scan and was kept constant until the last MRI scan. NCs were excluded also if presenting a past history or a current diagnosis of axis I psychiatric disorders. The study was approved by the University of Heidelberg's Institutional Review Board, and all subjects gave written informed consent.

2.2. ECT procedure

Right-sided unilateral (RUL) ECT was administered to patients with MDD and with SCZ three times per week using a Thymatron System IV system (Somatics LLC, Lake Bluff, IL, USA). NCs did not undergo ECT procedure. A brief pulse with square-wave stimulation with constant current was used. Stimulus intensity, was calculated during the first ECT session using a current that was 2.5-times higher than the seizure threshold (determined by repeated administration of stimuli of increasing intensity) and able to sustain an adequate

seizure duration, defined as the minimum current that resulted in a seizure activity of at least 25 s on the electroencephalogram. The total number of individual ECT sessions was determined by clinical response to ECT, i.e. administration was performed until remission (HAM-D ≤ 7 for MDD or eight core PANSS symptoms score ≤ 3 for SCZ, Andreasen et al., 2005) was achieved or until no further clinical improvement occurred. Patient response to ECT treatment was present in 7 patients with MDD (HAM-D reduction $\geq$ 50%) and in 6 patients with SCZ (PANSS reduction $\geq$ 25%), respectively. The maximum number of ECT sessions was 15. Anesthetic management included body weight-adapted etomidate followed by succinylcholine for muscle relaxation. Blood pressure, heart rate and oxygen saturation were continuously monitored. During the ECT-procedure, patients were oxygenated with a disposable bag and mask.

2.3. Image acquisition and preprocessing

Blood-Oxygen-Level-Dependent (BOLD)-fMRI was performed on a 3 T Siemens MAGNETOM Tim Trio MRI system equipped with a 12-channel phased-array head coil (Siemens, Erlangen, Germany). A gradient echo BOLD-EPI sequence was used to acquire 180 images at rest with eyes closed. Each image consisted of 30 4.5-mm-thick axial slices covering the entire brain (TR/TE=2000/30 ms; field of view=224 cm; matrix, 64×64; flip-angle=76). A baseline scan was performed within 5 days prior to the first ECT session and the post-ECT scan within 6–8 days after the last stimulation, with an average pre/post scan time of 37.6 (SD=7.5) and 36.3 (SD=4.2) for patients with MDD and SCZ ($p = 0.66$), respectively. A T1-weighted 3D image magnetization prepared rapid gradient echo (MP-RAGE) pulse sequence with isotropic spatial resolution of 1 mm3 (matrix= $256 \times 256 \times 192$, TR/TE=1570/2.74 ms; flip angle= 151) was also acquired. NCs had a single scanning session.

Imaging data were preprocessed using Data Processing Assistant for Resting-State fMRI version 3.0 (DPARSF, Chao-Gan and Yu-Feng, 2010). Briefly, all functional volumes were realigned to the first volume acquired and averaged to create a mean image. This mean functional image was used to estimate spatial normalization parameters to gray matter (GM) images obtained from T1 images. Realigned images were then normalized to the Montreal Neurological Institute (MNI) standard brain with a resulting voxel size of $3 \times 3 \times 3$ mm3. Spatial smoothing was carried out with a 6-mm full width half maximum isotropic 3D Gaussian kernel. Structural data were processed using the voxel-based morphometry approach using the unified model.

2.4. Independent component analysis (ICA)

A group of spatial Independent Component Analysis (ICA) was performed on preprocessed fMRI data using the Group ICA of fMRI Toolbox [GIFT4.0a; http://icatb.sourceforge.net] as described elsewhere (Sambataro et al., 2010b). Based on previous literature indicating high dimensionality ($n = 75$) of resting state fMRI data (Allen et al., 2011), we set the model order of ICA decomposition to 75 components and performed a two-step Principal Component Analysis (PCA). Group ICA was calculated on reduced data using the Infomax algorithm that resulted in 75 independent components (ICs) consisting of group spatial maps of IC loadings and related time courses (TC), which were included in the mixing matrix. Group-estimated ICs were then back-reconstructed to individual subject IC maps using a GICA3, which is a recent accurate back-reconstruction approach in terms of reconstructing the group aggregate spatial maps (Erhardt et al., 2011). Individual subject's linearly detrended TCs and maps were scaled using Z-scores. For each participant, a IC spatial map included voxel-wise IC loadings that represent local strength of functional connectivity and reflect the correspondence between the estimated TC in each voxel for each individual and the average TC of the aggregate network itself. All the ICs were screened for reliability via ICASSO toolbox using a stability index greater than 0.90 calculated by 100 bootstrapped permutated estimations of the ICs ($n = 10$ removed) and for artifactual patterns defined by those ICs with a spatial correlation $R^2 \geq 0.05$ with WM ($n = 3$ removed) and for CSF ($n = 6$ removed) and $R^2 \leq 0.005$ with GM ($n = 18$ removed). Additionally, ICs were inspected for known vascular, ventricular, motion and susceptibility artifact ($n = 5$ removed) (Allen et al., 2011). The screening procedure resulted in 33 intrinsic networks (INs, i.e. non-artifactual ICs estimated at rest), each with an individual spatial map and a TC. From INs, the following outcome measures were estimated per each subject: 33 spatial maps (SM), 33 spectra, and one between-functional networks connectivity (FNC). To increase the representativity of the spatial maps, only those voxels exceeding a t-score $>$ mean + 4 standard deviations were included in the analyses (Allen et al., 2011). INs were labeled using GIFT labeling tool that is based on a 14 resting state networks atlas (http://findlab.stanford.edu/functional_ROIs.html) derived from 90 regions of interest (Shirer et al., 2012). Spectra were estimated from detrended TCs using the multitaper method and split into 150 bins. Detrended TCs were despiked using 3dDeSPIKE algorithm (https://afni.nimh.nih.gov/pub/dist/doc/program_help/3dDespike.html), low-pass filtered (cut-off=0.15 Hz) and pairwise correlated. Finally, the FNC consisted of a 33×33 cross-correlation matrix of z-transformed pairwise correlations between TCs.

2.5. Statistical analysis

A multivariate analysis of covariance (MANCOVA) implemented in GIFT4.0a was used to identify the effects of variables on each response matrix (Allen et al., 2011). To reduce the large dimensionality and autocorrelation of the features, each response matrix (i.e., thresholded spatial maps, log-transformed spectra, and z-transformed FNC) underwent a 10-component PCA decomposition before entering the MANCOVAs. For each response matrix, separate backward-stepwise selection procedures were used to test the significance of reduced model. The following variables were tested: diagnostic group (NCs, pre-ECT patients, post-ECT patients) as predictor, and demographics (age and gender), structural (warping) or movement factors as nuisance variables. The warping extent during spatial normalization was estimated using the correlation between each subject's mean normalized image and the gradient echo EPI template provided in Statistical Parameter Mapping software (SPM, www.fil.ion.ucl.ac.uk/spm). Motion was estimated using frame-wise displacement (FD) that was calculated as the difference between the sum of the translation and rotation displacements (estimated during the realignment process) of one frame with respect to the previous one (Power et al., 2012); and root mean squared head position change, computed as the square root of the sum of the squared translation parameters relative to the first volume (Van Dijk et al., 2012). To yield a normal distribution, age and motion variables were log-transformed, and warping extent was z-transformed. Since MANCOVA in GIFT does not allow mixed models, we used a two-stage approach to identify treatment and diagnosis effect on response matrices: 1) exploratory MANCOVA with diagnostic group predictor incorporating both treatment and diagnosis effect; 2) confirmatory planned univariate analyses on reduced response matrices to identify the effects of diagnosis and treatment for each INs. Two sample t-tests (pre-ECT patients vs NCs) were used to test the effects of diagnosis, and paired t-tests (pre- vs post-ECT patients) were used to identify effects of ECT in patients, respectively. Correction for multiple comparisons was implemented using the false discovery rate (FDR) approach with α=0.05. For the SMs, significant clusters were identified using an uncorrected voxel-wise threshold of $p<0.001$, with a family-wise error rate at $p<0.05$ at the cluster level. For FNC, a global effect of

diagnosis on FNC networks was calculated on the FNC correlations averaged across the 7 FNC network domains using an omnibus test, followed by univariate tests. To identify the association between connectivity and treatment, signal from clusters showing a significant effect of treatment was separately correlated using Spearman's ρ with severity changes of HAM-D (for MDD) and PANSS total scores (for SCZ), respectively. Given previous evidence of altered interplay between EXE, DMN and SAL networks (see before), we investigated the effects of ECT (pre- vs post-ECT) connectivity differences in patients in these networks and corrected for the number of univariate paired t-tests performed on pairwise FNC connectivity ($n = 3$: EXE-DMN, DMN-SAL, EXE-SAL) and used a more stringent Bonferroni correction ($p = 0.017$) to achieve a corrected $p = 0.05$. All coordinates are reported in the Montreal Neurological Institute (MNI) system. Furthermore, exploratory analyses in each diagnosis subgroup were performed to investigate the effects of ECT treatment using two-tailed Wilcoxon signed-rank test.

3. Results

33 INs passed the quality control. Those INs encompassed the following brain networks: 2 within the auditory network, 4 within the striatal network, 6 within the DMN, 7 within the EXE (including 3 within the language network), 5 within the SAL, 2 within the sensory motor network, and 7 within the visual network (see Table S.1).

3.1. Effect of diagnosis

Multivariate analyses yielded significant differences for the effects of diagnosis in the SMs, in the spectra and in the FNC (see Fig. S.1). In particular, we found an effect of diagnosis on the SMs of the striato-thalamic network (IN12; t_{48}= 52.57, $p = 0.014$), and the DMN (IN62; t_{48}= 56.55, $p = 0.009$). Univariate analyses confirmed significantly lower IC loadings in the left pulvinar (x, y, z= −12, −24, 0, $k = 11$, $Z = 4.10$; Fig. 1.A) within the striato-thalamic network (IN12) in patients relative to NCs independently from the ECT treatment. The spectra of the striato-thalamic (IN02; t_{48}= 45.67, $p = 0.038$), the auditory (IN26; t_{48}= 64.47, $p = 0.002$), the visual (IN37; t_{48}= 46.14, $p = 0.033$), the EXE (IN59; t_{48}= 51.05, $p = 0.017$) and the SAL networks (IN23; t_{48}= 44.43, $p = 0.043$) were modulated by diagnosis. Univariate analyses indicated marginally greater low frequency oscillations (LFOs) in the 0.04–0.08 Hz frequency of a striatal network (IN02) in patients relative to NCs (t_{34}=1.88, $p = 0.06$).

FNC was modulated by diagnosis (omnibus test; t_{49}= 51.5211, $p = 0.0154$). In particular, network average FNC was reduced in visual (t_{49}= 3.81, $p = 0.001$) and sensorimotor (t_{49}=2.62, $p = 0.012$) networks, between-network FNC was reduced in the striatal-visual (t_{49}= 3.81, $p = 0.001$), visual-auditory (t_{49}=3.73, $p = 0.001$), DMN-visual (t_{49}=5.19, $p = 0.001$) and DMN-striatal (t_{49}= 3.62, $p = 0.001$) connectivity in patients relative to NCs.

3.2. Effect of ECT treatment

3.2.1. All patients

ECT treatment resulted in increased IC loadings in the medial prefrontal cortex (mPFC, $x = 9$, $y = 45$, $z = 18$, $k = 24$, $Z = 4.17$) within the DMN SM (IN 62; Fig. 3). LFOs in the 0.04–0.08 Hz frequency were reduced by ECT treatment in the striato-thalamic (IN02, t_{15} =4.01, $p = 0.001$, Fig. 2.B) as well as in the visual network (IN37; t_{15} =2.52, $p = 0.023$). Univariate analyses on the FNC revealed a reduced EXE-DMN connectivity (IN42-IN51, t_{15} =3.95, $p = 0.001$) as well as increased EXE-SAL connectivity (IN59-IN36, $t_{15} = 3.43$, $p = 0.003$, Fig. 4.A). FNC reduction in the EXE-DMN connectivity showed a trend for inverse correlation with EXE-SAL connectivity increase ($\rho = -0.47$, $p = 0.06$, Fig. 4.B). We did not find any response matrix difference between MDD and SCZ.

3.2.2. SCZ only

ECT treatment resulted in significantly increased IC loadings in the medial prefrontal cortex within the DMN SM in SCZ (IN 62, $Z = 2.47$, $p = 0.01$). The IC loading change following ECT treatment in mPFC did not show any correlation with PANSS-total score change in SCZ ($p > 0.2$). We did not find any difference in LFOs. Univariate analyses on the FNC revealed marginally reduced EXE-DMN connectivity (IN42-IN51, $Z = 1.76$, $p = 0.077$) as well as increased EXE-SAL connectivity (IN59-IN36, $Z = 1.76$, $p = 0.077$).

3.2.3. MDD only

ECT treatment resulted in marginally increased IC loadings in the medial prefrontal cortex within the DMN SM in MDD (IN 62, $Z = 1.76$, $p = 0.077$). The IC loading change following ECT treatment in mPFC showed no correlation correlated with HAM-D score change in MDD ($p > 0.2$). We did not find any difference in the LFOs. Univariate analyses on the FNC revealed marginally reduced EXE-DMN connectivity (IN42-IN51, $Z = 1.76$, $p = 0.077$) as well as increased EXE-SAL connectivity (IN59-IN36, $Z = 1.76$, $p = 0.077$).

4. Discussion

The aim of this study was the identification of transdiagnostic effects of ECT treatment on the functional network dynamics in patients with MDD and SCZ. At baseline patients showed reduced within-network connectivity in the pulvinar within a striato-thalamic network along with increased LFOs in a striatal IN relative to NCs. Within and between FNC was reduced across several INs including the DMN, visual, striatal and somatosensory networks. ECT resulted in increased functional connectivity of the DMN in the mPFC. Also, ECT reduced the LFOs of the striato-thalamic and visual networks. Furthermore, ECT treatment was associated with increased FNC between the executive and the salience networks as well as with its reduction between the executive and the DMN networks.

We found altered function in striatal networks in patients. First, within a striato-thalamic network functional connectivity was reduced in the pulvinar in patients before ECT. This thalamic nucleus has dense connections with subcortical and cortical regions and plays a role in mediating vision, cognitive and emotional processing which may be altered in MDD and SCZ (Zhou et al., 2016). Dysfunction in the resting connectivity of this region has been reported for MDD (Hamilton et al., 2012), and SCZ (Penner et al., 2018) and is thought to be related with altered

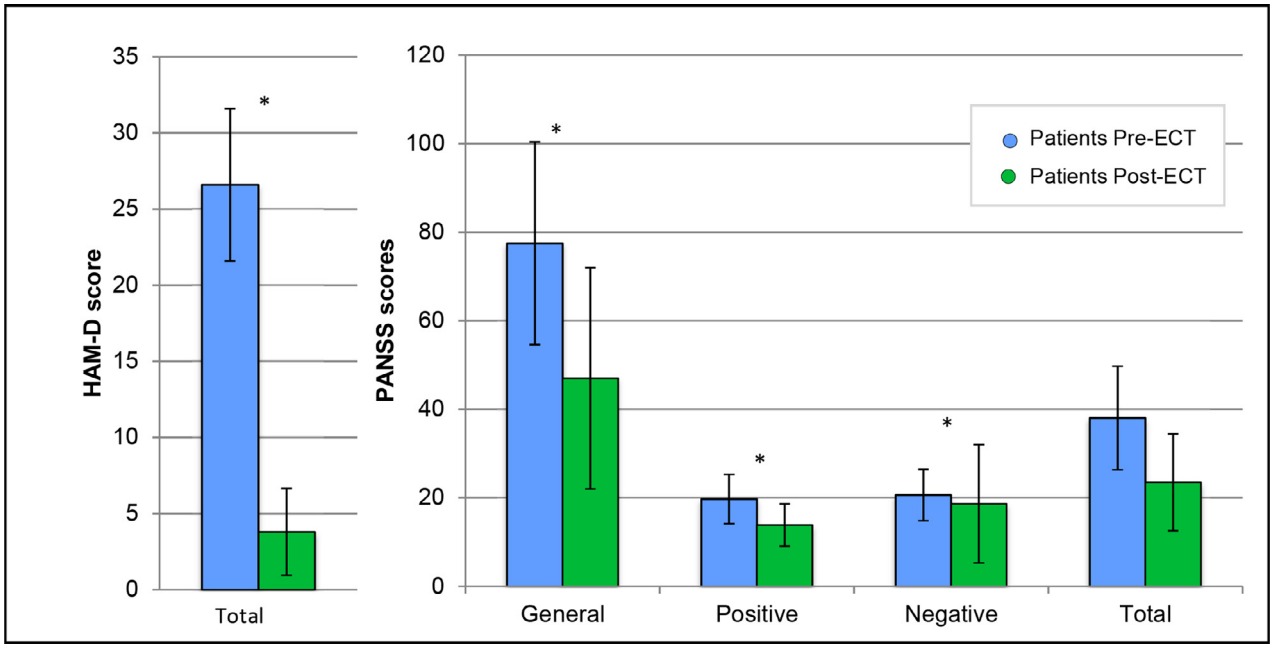

Fig. 1 Clinical severity and ECT treatment. Both patients with Major Depressive Disorder (HAM-D) and patients with Schizophrenia (PANNS) had a significant clinical improvement after the ECT treatment. ECT, electroconvulsive therapy; HAM-D, Hamilton Rating Scale for Depression; PANNS, Positive and Negative Syndrome Scale. Pre- and post-ECT mean severity scores are indicated in blue and in green, respectively. Error bars indicate the standard deviation. *, indicates $p<0.01$, two-sample t-test.

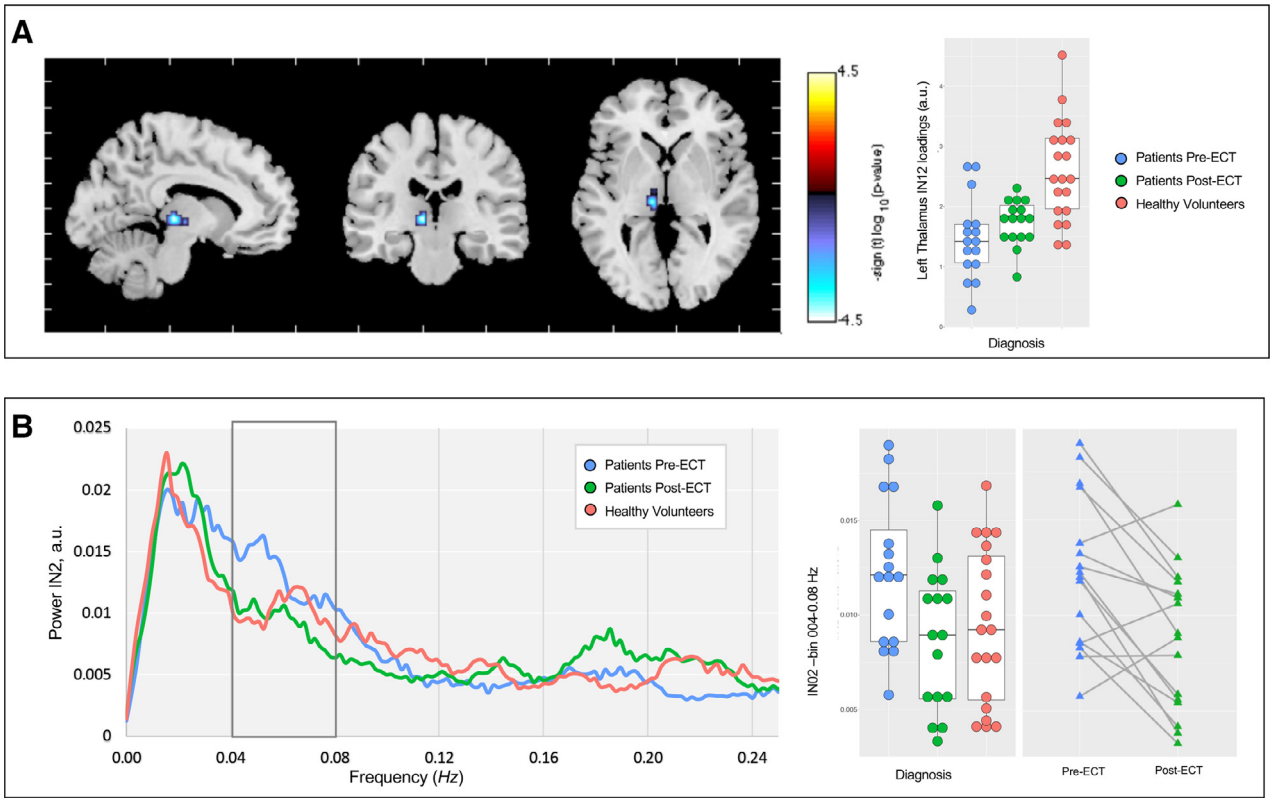

Fig. 2 Brain regions and spectra showing significant differences between patients and normal controls at baseline. IC loadings in the left pulvinar (IN12) were greater in controls relative to patients at baseline (A). Low frequency oscillations (LFO) in the striatal network (IN2) were greater in patients relative to controls at baseline (B). Also, LFOs in the IN2 were reduced following ECT treatment as displayed in the spaghetti plot (B, right panel). Color bar indicates -sign(t)*log10(p-value) for the patients>normal controls. $p<0.05$, FDR corrected.

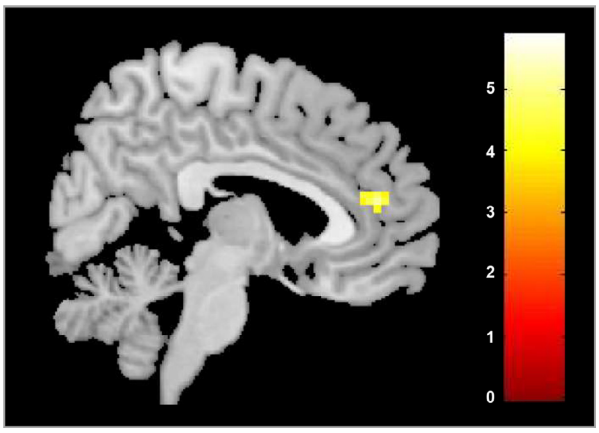

Fig. 3 ECT treatment increased IC loadings of the DMN (IN62) in the medial prefrontal cortex (mPFC) in patients with MDD and SCZ. Color bar indicates T values for the ECT treatment >baseline contrast of a paired t-test in patients.

emotional attention. Recent studies showed an association between antidepressant effects and increased functional connectivity of the pulvinar (Kraus et al., 2018). However, ECT treatment did not show a significant change in this parameter in our study. In a striatal network spanning only across the basal ganglia we found increased LFOs in patients and this measure was modulated by ECT. LFOs have been interpreted as reflecting spontaneous variation of brain activity over time and are thought to coordinate large-scale network regions activity, thus mediating functional connectivity (Drew et al., 2008). The striatum has been consistently implicated in the pathophysiology of both SCZ (Sorg et al., 2013) and MDD (Phillips et al., 2003) with a role on stimulus salience, emotional and reward processing. In particular, altered LFOs in the striatum were reported in SCZ (Hoptman et al., 2010) as well as in MDD (Sambataro et al., 2017) and correlated with disease severity (He et al., 2013; Zhang et al., 2017), thus suggesting that altered striatal connectivity may underlie both disorders.

Furthermore, ECT modulated the striatal network spanning across all the basal ganglia. Notably, the LFOs within this network, that were increased in patients before ECT, were reduced and normalized with this treatment. Interestingly, antipsychotic treatment with risperidone in drug naïve first episode SCZ has been shown to affect LFOs in the striatum, with lower LFOs being associated with better response (Hu et al., 2016). Also, early antidepressant response to escitalopram was predicted by increased caudate LFOs (Cheng et al., 2017), thus supporting a role of the striatum function in mediating treatment response.

ECT regulated also DMN and internetwork connectivity. Connectivity in the mPFC was increased after ECT treatment. Previous studies have shown that ECT modulated DMN connectivity in MDD (Leaver et al., 2016; Li et al., 2013). We have also shown that olanzapine monotherapy in SCZ can increase DMN connectivity and specifically in mPFC (Sambataro et al., 2010a). This region is the anterior hub of the DMN and plays an important role in mediating self-referential cognitive, social and emotional processing which may be altered in both MDD and SCZ (Whitfield-Gabrieli and Ford, 2012). The activity of the DMN is anticorrelated with that of the EXE and their interplay is mediated by the SAL in the so-called 'triple network model', which has been implicated in several psychiatric disorders, including MDD and SCZ (Menon, 2011). The salience of an event can trigger the activity of the SAL that acts like a switch, turning on the EXE and off the DMN, respectively, thus promoting goal-directed behavior. When the functional coupling between EXE and ventral DMN increases, their activities may

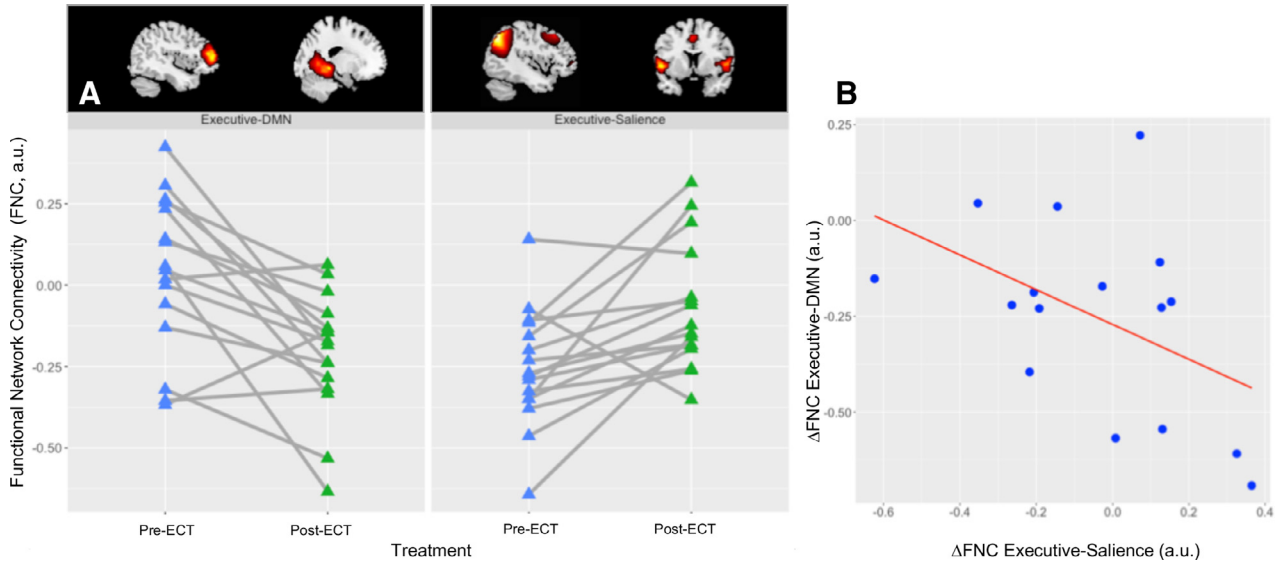

Fig. 4 ECT treatment modulates Functional Network Connectivity (FNC). The FNC between Executive (IN42) and DMN (IN51) networks was reduced (A, left panel), whereas the FNC between the Executive (IN59) and Salience (IN36) networks was increased (A, right panel), by ECT, respectively. The magnitude of FNC changes in these networks was negatively correlated (B). Brain maps depict the spatial extent of the mean INs (from the left: Executive, IN42; Default Mode Network, DMN; IN51; Executive, IN59; Salience, IN36). a.u., arbitrary units.

become synchronous and may interfere and impair cognitive and emotional processing according to the so called 'default mode interference' hypothesis (Sambataro et al., 2010b). Furthermore, reduced coupling between SAL and EXE may contribute to altered salience attribution to external stimuli and internal states as well as to dysfunctional switching of the EXE network (Sambataro et al., 2017). Overall, ECT may contribute to the clinical improvement in MDD and SCZ via its effects on all the three large-scale networks that control behavior: First, increasing the anticorrelation between antagonistic networks (EXE-DMN), thus fine tuning the cortical signals as previously showed for transcranial magnetic stimulation (Liston et al., 2014); Second, improving the modulation of the network switch on the behavioral-controlling network (EXE-SAL). Notably, these two ECT-dependent changes were inversely correlated, further suggesting a rebalancing function of this neurostimulation technique. Lastly, the DMN changes in mPFC can also contribute to this effect via a direct effect on the FC of this network.

The molecular mechanisms underlying ECT remain still unknown. Studies in rodents, non-human primates and patients with Parkinson's disease have suggested the idea that ECT modulates dopamine signaling (Costain et al., 1982; Douyon et al., 1989; Landau et al., 2011), and particularly D2/D3 (Dannlowski et al., 2013). Since dopamine system, although different in its characteristics, is crucial in the pathophysiology of both MDD and SCZ (Grace, 2016), alterations of this signaling may contribute to ECT-dependent clinical improvement. Remarkably, the ECT-induced changes that we identified in our study in striatal and DMN networks largely overlap with those following the administration of psychotropic drugs (olanzapine and escitalopram) that can modulate dopamine signaling (Cheng et al., 2017; Sambataro et al., 2010a), and with the effects of genetic variation in dopamine D2 pathway (Sambataro et al., 2013). Overall, our findings lend support for a shared role of dopamine signaling modulation in mediating ECT treatment effects in both MDD and SCZ.

Some limitations have to be acknowledged in our study, such as the sample size, medication effects and clinical assessment. We had a modest number of subjects that limited our ability to discern neural effects of ECT between patient groups. Nonetheless, we used rigorous methods of multiple comparisons corrections thus providing an adequate control of type I errors. The patients included in this study for the severity of their disorder continued their psychotropic treatment, thus not allowing the estimation of direct effects of the medication. However, the drug regimen was kept constant throughout the study, thus limiting the confounding effects of pharmacological treatment on the estimation of the changes of neural activity due to ECT. Also, symptom evaluation with respect to ECT treatment timing, although not critical for evaluating connectivity differences, was not blinded to clinicians, thus limiting the reliability of this measure and possibly contributing to the lack of brain behavior correlation.

5. Conclusions

We have shown that ECT can modulate functional coupling within the DMN and striatal networks in both patients with MDD and SCZ. Also, the between network connectivity across EXE, SAL and DMN can be modulated by ECT, thus recalibrating the interplay of these networks. Our findings highlight the importance of the function dynamics of large-scale networks beyond the classical limbic system that has been proposed so far. They extend the validity of transnosological approaches also for the identification of common mechanism of treatment. Future studies should identify functional connectivity network indexes predicting ECT response that could be used as treatment selection biomarkers for a more targeted and efficient precision medicine.

CRediT authorship contribution statement

Fabio Sambataro: Conceptualization, Investigation, Methodology, Supervision, Visualization, Writing - original draft, Writing - review & editing. **Philipp Arthur Thomann:** Conceptualization, Data curation, Investigation, Methodology, Writing - original draft, Writing - review & editing. **Henrike Maria Nolte:** Investigation, Writing - review & editing. **JH Hasenkamp:** Investigation, Writing - review & editing. **Dusan Hirjak:** Investigation, Writing - original draft. **Katharina M. Kubera:** Investigation, Writing - review & editing. **Stefan Hofer:** Investigation, Writing - review & editing. **Ulrich Seidl:** Investigation, Writing - review & editing. **Malte Sebastian Depping:** Investigation, Writing - review & editing. **Klaus Maier-Hein:** Conceptualization, Investigation, Methodology, Writing - review & editing. **Robert Christian Wolf:** Conceptualization, Data curation, Investigation, Methodology, Supervision, Writing - original draft, Writing - review & editing.

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Conflict of interest

All the authors declare that they have no conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2019.06.002.

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