European Neuropsychopharmacology (▮▮▮▮) ▮, ▮▮▮–▮▮▮

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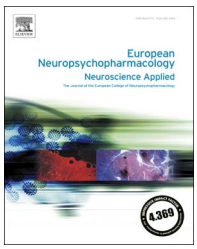

EEG connectivity between the subgenual anterior cingulate and prefrontal cortices in response to antidepressant medication

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Received 3 November 2016; received in revised form 6 February 2017; accepted 9 February 2017

KEYWORDS
EEG;
MDD;
Connectivity;
Antidepressants;
State;
Trait

Abstract
Antidepressant medication is the most common treatment for major depressive disorder (MDD), however, the precise working mechanism underlying these treatments remains unclear. Recent neuromodulation treatments demonstrate that direct stimulation of the dorsolateral prefrontal cortex (DLPFC), dorsomedial prefrontal cortex (DMPFC), and subgenual anterior cingulate (sgACC) relate to clinical improvement, suggesting connectivity alterations of the DLPFC-DMPFC-sgACC network to mediate antidepressant response. The international Study to Predict Optimized Treatment in Depression (iSPOT-D) is an international multicentre study that collected EEG data for 1008 MDD patients, randomized to 3 different antidepressant medications (N=447 MDD with complete pre- and post-treatment data and N=336 non-MDD). Treatment response was defined by a decline of >50% on the Hamilton Rating Score for Depression ($HRSD_{17}$). We investigated whether connectivity in alpha and theta frequencies of the DLPFC-DMPFC-sgACC network changed from pre- to post-treatment between: (i) patients and controls, and (ii) responders (R) and non-responders (NR). Women exhibited higher alpha

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http://dx.doi.org/10.1016/j.euroneuro.2017.02.002

and theta connectivity compared to males, both pre- and post-treatment. Furthermore, theta, but not alpha, hypo-connectivity was found for MDD patients. A decreased alpha connectivity after treatment was found only for male responders, while non-responders and females exhibited no changes in alpha connectivity. Decreasing alpha connectivity could potentially serve as a treatment emergent biomarker, in males only. Furthermore, it could be useful to *a priori* stratify by gender for future MDD studies.

1. Introduction

Major depressive disorder (MDD) is a chronic mental disease with a remitting and relapsing course. Despite the variety of available treatments, up to 40–50% of patients fail to respond (Kessler and Bromet, 2013). The use of antidepressant medication is a first-line treatment for MDD, in particular the use of selective serotonin reuptake inhibitors (SSRI's) and serotonin-norepinephrine reuptake inhibitor (SNRI's). Despite widespread use, the exact working mechanism behind these treatments is not clear. New treatments such as repetitive Transcranial Magnetic Stimulation (rTMS) and Deep Brain Stimulation (DBS) are emerging (Fox et al., 2012; Liston et al., 2014). These new treatments directly targeted key structures in depression such as the dorsolateral prefrontal cortex (DLPFC) (George et al., 2010; O'Reardon et al., 2007), the dorsomedial prefrontal cortex (DMPFC) (Downar and Daskalakis, 2013; Downar et al., 2014) and the subgenual cingulate cortex (sgACC) (Mayberg et al., 2005) and thereby have shown that direct stimulation of these regions is associated with clinical improvement. Recent insights into how these neuromodulation treatments work suggest network connectivity changes within a DLPFC-DMPFC-ACC network to mediate antidepressant response (Fox et al., 2012; Liston et al., 2014), and are also possibly implicated in pharmacological treatments.

The convergent evidence of involvement of these structures indicates that they are likely to be important hubs in the networks that modulate depression. The sgACC and sections of the DMPFC are components of the default mode network while the DLPFC is partly implicated in the central executive network (CEN). A deficit in switching between the DMN and CEN is well known in depression (Liston et al., 2014; Sridharan et al., 2008) and is considered to be one of the main reasons behind cognitive dysfunction in depression. The DLPFC has been described to be hypoactive in depression (Korgaonkar et al., 2013), and an increase in fMRI activity of this structure is associated with treatment response (Fitzgerald et al., 2006; Koenigs and Grafman, 2009). Contrary to the DLPFC, the sgACC has been described to be hyperactive in depression, along with hyperconnectivity to other parts of the DMN observed with PET scans and with fMRI (Liston et al., 2014; Mayberg et al., 2005), and a decrease in activity of the sgACC is associated with antidepressant response (Koenigs and Grafman, 2009; Mayberg et al., 2005). The DMPFC, or dorsal nexus, is a core region to multiple networks, including the DMN, CEN and salience network (SN), with increased fMRI connectivity to all three networks in depression (Sheline et al., 2010). The DMPFC has been observed to be abnormally activated during positive and negative affect processing in MDD, which normalizes after successful treatment (Bermpohl et al., 2009; Dunlop et al., 2016; Mayberg et al., 1999). As rTMS is limited to cortical surfaces, it is hypothesized that DLPFC-rTMS (and DMPFC-rTMS) might exert its antidepressant effect via trans-synaptic connectivity to deeper regions, such as the sgACC (Fox et al., 2012, 2014; George et al., 1995, 1997; Padberg and George, 2009). Serotonergic challenge has been observed to reduce intrinsic functional connectivity in brain regions implicated in mood regulation (Anand et al., 2005, 2007), such as the ventral anterior cingulate cortex (vACC, which includes the sgACC/Cg25 and the rACC/Cg24) and limbic structures such as the amygdala (Drevets et al., 2008; Gudayol-Ferré et al., 2015). However, the full scope of serotonergic and antidepressant action on functional connectivity in the human brain, especially with respect to the DLPFC-DMPFC-ACC network, has not been explored widely.

The international Study to Predict Optimized Treatment in Depression (iSPOT-D) is a multicentre study aimed at finding biomarkers for antidepressant treatment response (Williams et al., 2011). Preferably these biomarkers need to be cost-effective and EEG measurements represent an attractive modality due to the relatively low cost and burden imposed on patients, and informative about underlying brain circuits. To this goal, the study collected EEG data from 1008 MDD patients, randomized to 3 different antidepressant medications, prior to and after 8 weeks of treatment. 336 controls also completed EEG data collection at baseline and at 8 weeks. The aim of this manuscript is to investigate connectivity changes in the DLPFC-DMPFC-sgACC network across 8 weeks of treatment, not only for patients and controls, but also comparatively for antidepressant responders and non-responders, and thus to investigate whether these connectivity differences are state, trait or medication related. To this goal, we explored baseline to post-treatment connectivity changes between responders and non-responders to medication in alpha and theta EEG frequencies, as previous studies using the same sample as the current study have found the most relevant differences in alpha and theta (Arns et al., 2015a, 2015b, 2016). Gender was included as a factor because previous iSPOT-D studies have demonstrated clear qualitative gender differences in topographic distribution of EEG activity and gender-specific predictors of treatment response of alpha asymmetry (Arns et al., 2016) and Event Related Potentials (van Dinteren et al., 2015). Quantitative differences could be resolved by using gender as a covariate, however the clear qualitative differences warrant *a priori* stratification by gender rather

Please cite this article as: Iseger, T.A., et al., EEG connectivity between the subgenual anterior cingulate and prefrontal cortices in response to.... European Neuropsychopharmacology (2017), http://dx.doi.org/10.1016/j.euroneuro.2017.02.002