Journal of Psychiatric Research 73 (2016) 108–115

Contents lists available at ScienceDirect

Journal of Psychiatric Research

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

CNS- and ANS-arousal predict response to antidepressant medication: Findings from the randomized iSPOT-D study

Sebastian Olbrich [a, g, *], Anja Tränkner [a], Galina Surova [a], Richard Gevirtz [b], Evian Gordon [c, d], Ulrich Hegerl [a], Martijn Arns [e, f]

[a] Dept. of Psychiatry and Psychotherapy, University of Leipzig, Germany
[b] Alliant International University, San Diego, CA, USA
[c] Brain Resource Ltd, Sydney, NSW, Australia
[d] Brain Resource Ltd, San Francisco, CA, USA
[e] Dept. of Experimental Psychology, Utrecht University, Utrecht, The Netherlands
[f] Research Institute Brainclinics, Nijmegen, The Netherlands
[g] Dept. of Psychiatry, Psychotherapy and Psychosomatic, University Zürich, Switzerland

ARTICLE INFO

Article history:
Received 22 June 2015
Received in revised form
4 December 2015
Accepted 4 December 2015

Keywords:
iSPOT-D
CNS-arousal
EEG-Vigilance
Heart rate
Antidepressant
Major depressive disorder

ABSTRACT

Arousal systems are one of the recently announced NIMH Research Domain Criteria to inform future diagnostics and treatment prediction. In major depressive disorder (MDD), altered central nervous system (CNS) wakefulness regulation and an increased sympathetic autonomic nervous system (ANS) activity have been identified as biomarkers with possible discriminative value for prediction of antidepressant treatment response. Therefore, the hypothesis of a more pronounced decline of CNS and ANS-arousal being predictive for a positive treatment outcome to selective-serotonin-reuptake-inhibitor (SSRI) treatment was derived from a small, independent exploratory dataset (N = 25) and replicated using data from the randomized international Study to Predict Optimized Treatment Response in Depression (iSPOT-D). There, 1008 MDD participants were randomized to either a SSRI (escitalopram or sertraline) or a serotonin-norepinephrine-reuptake-inhibitor (SNRI-venlafaxine) arm. Treatment response was established after eight weeks using the 17-item Hamilton Rating Scale for Depression. CNS-arousal (i.e. electroencephalogram-vigilance), ANS-arousal (heart rate) and their change across time were assessed during rest. Responders and remitters to SSRI treatment were characterized by a faster decline of CNS-arousal during rest whereas SNRI responders showed a significant increase of ANS-arousal. Furthermore, SSRI responders/remitters showed an association between ANS- and CNS-arousal regulation in comparison to non-responders/non-remitters while this was not the case for SNRI treatment arm. Since positive treatment outcome to SSRI and SNRI was linked to distinct CNS and ANS-arousal profiles, these predictive markers probably are not disorder specific alterations but reflect the responsiveness of the nervous system to specific drugs.

1. Introduction

Recently, the United States National Institute of Mental Health (NIMH) has introduced the Research Domain Criteria (RDoC) project which is aimed to transform clinical syndrome-based diagnosis into an individualized framework of psychophysiology to support the diagnostic process of mental disorders (Insel et al., 2010). The major RDoC domains include the arousal/modulatory systems as separate criteria to inform transdiagnostic approaches and therapeutic/diagnostic decisions. In this study we will investigate how arousal/modulatory research domains are associated with antidepressant treatment outcome in major depressive disorder (MDD).

For all higher order organisms, the behavior and interaction with its environment are profoundly influenced by regulation of central nervous system (CNS) arousal (Hegerl and Hensch, 2012) and autonomic nervous system (ANS) arousal (Head, 1923). Maladaptive behavior as can be found in psychiatric disorders might

* Corresponding author. Clinic for Psychiatry, Psychotherapy and Psychosomatic, University Zürich, Lenggstrasse 31, Postfach, 1931 8032 Zürich, Switzerland.
E-mail address: Sebastian.olbrich@puk.zh.ch (S. Olbrich).

http://dx.doi.org/10.1016/j.jpsychires.2015.12.001
0022-3956/

hence reflect alterations in these global regulatory systems (Hegerl and Hensch, 2012). In MDD, the discussion about altered CNS-arousal and wakefulness-regulation as contributing factors for the disorder has been sparked by findings of disturbed sleep architecture (Arfken et al., 2014; Hoffmann et al., 2000; Lopez et al., 2010; Olbrich and Arns, 2013; Reynolds et al., 1985; Rotenberg et al., 2002) and the antidepressant effects of sleep-deprivation and chronobiological treatments (McClung, 2013). Facilitated by the clinical finding of disturbed sleep initiation in the majority of MDD patients, a conceptual framework has been proposed that links behavioral core dysfunction in MDD such as sleep disturbances and withdrawal from arousing environments to an increased cortical tonic arousal (Hegerl and Hensch, 2012). The symptoms of the disorder hence are interpreted as a counter-regulating mechanism to this elevated CNS-arousal.

Following this hypothesis, Hegerl et al. (Hegerl et al., 2011) demonstrated elevated CNS-arousal in patients suffering from MDD in comparison to healthy controls during resting electroencephalogram (EEG), a finding that was replicated by Olbrich et al. (Olbrich et al., 2012). Although several studies have reported greater resting state EEG-alpha power in responders to antidepressant medication than in non-responders (Bruder et al., 2001; Tenke et al., 2011; Ulrich, 1987), the predictive power of CNS-arousal regulation has not been addressed so far.

Further there is also a strong linkage between the activity of the ANS and mood symptoms (Brown et al., 2009). MDD is an independent risk factor for myocardial infarction and coronary heart disease (Nicholson et al., 2006) and patients with cardiovascular diseases show increased rates of MDD (Egede, 2007). Therefore the activity of the ANS, including a possible hyper activation of the sympathetic branch thereby seems to play a crucial role in the linkage of cardiovascular and mood symptomatology (Carney et al., 2005). In line with this, several studies report a shift toward an increased sympathetic and decreased parasympathetic activity in MDD (Brunoni et al., 2013; Kemp et al., 2010). Although some studies report of a predictive value of heart rate variability (HRV) in the treatment of MDD (Fraguas et al., 2007; Jain et al., 2014), no study to our knowledge exists that examined the predictive power of the heart rate (HR), which has been proven to be a reliable measure of ANS-function (Grassi et al., 1998).

In healthy subjects a tight interaction of ANS- and CNS arousal exists. During the resting state, high sympathetic activity is associated with a high CNS-arousal and high parasympathetic activity with low CNS-arousal (Olbrich et al., 2011). However, disturbances of the interaction between ANS-function and CNS-arousal in MDD have not been systematically investigated.

Following the above findings, the first goal of this study was to analyze whether successful antidepressant treatment (response or remission) with a selective-serotonin-reuptake-inhibitor (SSRI) in contrast to treatment failure (non-response or non-remission), is associated with differences in CNS-arousal (defined by EEG-vigilance) and ANS-arousal (defined by HR).

Further, different classes of antidepressant medications have been reported to evoke distinct changes in arousal function (Kemp et al., 2010; Licht et al., 2010). Thus a secondary goal was to investigate whether CNS- and ANS-arousal profiles differed for treatment outcome following treatment with SSRIs or with serotonin-norepinephrine-reuptake-inhibitors (SNRIs), pointing out a possible discriminative value for the choice of medication.

For generation of hypothesis about the direction of changes, a first small and independent dataset was analyzed by means of arousal function and SSRI treatment outcome. Then data from the multi-center, randomized, prospective open-label international Study to Predict Optimized Treatment Response in Depression (iSPOT-D) (see(Arns et al., 2015; Williams et al., 2011) for details) was used for confirmation of CNS- and ANS-arousal markers in the prediction of SSRI treatment outcome. Further, an exploratory analysis aimed at differences of CNS and ANS-arousal parameters in responder/remitters (non-responders/non-remitters respectively) during SSRI and SNRI treatment was carried out.

2. Materials and methods

2.1. Design, participants and treatment

2.1.1. Exploratory dataset

The exploratory first dataset consisted of 23 patients with MDD recruited at the university hospital Leipzig, Germany. All subjects were unmedicated at baseline and treated with a SSRI (escitalopram or sertraline). Re-evaluation of depressive symptoms was done after two weeks using the 17-item Hamilton Rating Scale for Depression ($HRSD_{17}$). Since a two-week interval is quite short to lead to a reduction of 50% in $HRSD_{17}$, response was defined as a reduction of only >33% in $HRSD_{17}$ in this exploratory dataset.

2.1.2. iSPOT-D dataset

In the second dataset from the international multi-center, randomized, prospective open-label trial (Phase-IV clinical trial), MDD participants were randomized in equal parts to escitalopram, sertraline or venlafaxine-extended release.

After screening 6693 patients for eligibility, 1008 were enrolled (Fig. 1 shows more detail of this trial see (Williams et al., 2011)). Diagnosis of non-psychotic MDD (allowing comorbid anxiety disorders) was confirmed before randomization at the baseline visit using the Mini-International Neuropsychiatric Interview (MINI-Plus) (Sheehan et al., 1998), according to DSM-IV criteria, and a score $\geq$16 on the $HRSD_{17}$. All participants were drug-naïve or underwent a sufficient washout period of at least five half-lives of the previously used medication. Remission was defined as a score of $\leq$7 and response as a >50% decrease in $HRSD_{17}$ score from baseline to week eight.

2.2. Ethics statement

The exploratory study and the iSPOT-study were approved by the institutional review boards at all of the participating sites and were conducted according to the principles of the Declaration of Helsinki 2008. After study procedures were fully explained, participants provided written informed consent. The iSPOT trial was registered with ClinicalTrials.gov. Registration Number: NCT00693849; URL: http://clinicaltrials.gov/ct2/show/NCT00693849.

2.3. Pre-treatment assessments

Electroencephalogram (EEG) and electrocardiogram (ECG) were recorded during 15 min (exploratory dataset) or 2 min (iSPOT-data) resting state with eyes closed. Details of the reliability and across-site consistency have been published elsewhere (Williams et al., 2005). Participants were seated in a sound and light attenuated room with temperature of 22 °C to avoid arousal changes due to uncomfortable light or temperature. EEG data were acquired from 26 channels (extended international 10–20 system, averaged mastoid reference, AFz ground, impedance<5kOhms, sampling rate >500 Hz) with additional ECG (sampling rate >500 Hz) and electrooculogram (EOG) channels (horizontal and vertical).