Psychiatry Research xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Psychiatry Research

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

Enhanced error related negativity amplitude in medication-naïve, comorbidity-free obsessive compulsive disorder

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ARTICLE INFO

Keywords:
Obsessive-compulsive disorder
Error related negativity
Error monitoring
Cingulate cortex
Neurocognition

ABSTRACT

Error monitoring and response inhibition is a key cognitive deficit in obsessive-compulsive disorder (OCD). Frontal midline regions such as the cingulate cortex and pre-supplementary motor area are considered critical brain substrates of this deficit. Electrophysiological equivalent of the above dysfunction is a fronto-central event related potential (ERP) which occurs after an error called the error related negativity (ERN). In this study, we sought to compare the ERN parameters between medication-naïve, comorbidity-free subjects with OCD and healthy controls (HC). Age, sex and handedness matched subjects with medication-naïve, comorbidity-free OCD (N = 16) and Healthy Controls (N = 17) performed a modified version of the flanker task while EEG was acquired for ERN. EEG signals were recorded from the electrodes FCz and Cz. Clinical severity of OCD was assessed using the Yale Brown Obsessive Compulsive Scale. The subjects with OCD had significantly greater ERN amplitude at Cz and FCz. There were no significant correlations between ERN measures and illness severity measures. Overactive performance monitoring as evidenced by enhanced ERN amplitude could be considered as a biomarker for OCD.

1. Introduction

Structural and functional impairments of frontal-striatal circuitry have been considered etiologically important in obsessive-compulsive disorder (OCD) (Menzies et al., 2008; Marsh et al., 2014). These impairments have been postulated to translate into cognitive deficits that are critical in the understanding of the neurobiology of the illness (Menzies et al., 2008). Executive functions, especially, error monitoring and response inhibition might be crucial components of the neurobiological underpinnings of OCD. The symptom profile of OCD such as repetitive doubts, repeated actions and a "sense of incompleteness" indicates a pathophysiological role for hyperactive error signals (Pitman, 1987).

Electrophysiological equivalent of the above dysfunction is a fronto-central event related potential (ERP) that occurs after an error called the error related negativity (ERN) (Yeung et al., 2004). ERN is an ERP recorded typically within 50 msec after the occurrence of an incorrect response during fast response tasks involving conflict (Falkenstein et al., 2000). The source localization of ERN using simultaneous acquision of EEG with functional magnetic resonance imaging (fMRI) indicates that ERN is generated in the frontal midline structures, particularly the cingulate cortex and the pre-supplementary motor area (van Veen and Carter, 2002; Grutzmann et al., 2014). Larger amplitude of ERN in OCD has been demonstrated in previous studies (Endrass et al., 2010; Endrass and Ullsperger, 2014). ERN could, therefore, form an important biomarker of the illness in OCD. However, ERN can be affected by the medications taken by the patients. For instance, Endrass and colleagues reported that ERN amplitude was reduced in the subset of patients who were on selective serotonin reuptake inhibitors in comparison to those who were unmedicated (Endrass et al., 2008). It is also important to note that ERN may be abnormal in other psychiatric disorders such as anxiety disorders (Hajcak et al., 2003) and major depression (Chiu and Deldin, 2007) which are common comorbidities of OCD. Hence it is imperative to examine ERN in medication naïve and comorbidity free OCD patients.

In this study, we compared ERN in medication-naïve OCD patients and matched healthy controls. In addition, we sought to examine the clinical correlates of ERN in OCD. Based on the existing evidence, we hypothesized that medication-naïve OCD patients would have greater ERN amplitude compared to healthy controls. In addition, we also hypothesized that the amplitude of ERN among OCD patients would correlate positively with the severity of the illness.

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http://dx.doi.org/10.1016/j.psychres.2017.09.010
Received 16 August 2016; Received in revised form 3 August 2017; Accepted 8 September 2017

2. Materials and methods

2.1. Subjects and setting

The participants consisted of subjects with DSM-IV diagnosis of OCD (N = 16) who were never exposed to psychotropic medications and age and sex-matched volunteering healthy controls (N = 17). The OCD patients were recruited from the specialty OCD clinic at the National Institute of Mental Health And Neurosciences (NIMHANS), Bangalore, India. The study was carried out in accordance with the Declaration of Helsinki. The NIMHANS institute ethics committee approved the study. All participants gave written informed consent before the assessments. Subjects with OCD were never treated in the past with psychotropic medications.

2.2. Subject recruitment and instruments used

The diagnosis of OCD was made according to the DSM-IV criteria (APA, 1994). The Mini International Neuropsychiatric Interview (MINI version 5.0.0) was used to ascertain the diagnosis and to evaluate the presence of comorbid psychiatric conditions (Sheehan et al., 1998). None of the subjects with OCD had comorbid psychiatric or medical disorders. It was also ensured that the subjects did not have tic disorders as ascertained using the relevant sections from the MINI Kid (Sheehan et al., 1998). The participants with OCD were evaluated with the Yale-Brown obsessive compulsive scale (YBOCS) that includes a symptom checklist and a severity rating scale (Goodman et al., 1989). Hamilton Depression Rating scale (HDRS) (Hamilton, 1960) and Hamilton Anxiety Rating Scale (HARS) (Hamilton, 1959) were employed to measure the depressive and anxiety symptoms respectively for all the subjects. Healthy controls who volunteered for participation in the study, were recruited from consenting individuals from the community. Psychiatric morbidity in healthy controls was excluded by administering the MINI. None of the healthy controls had history of medical illnesses or substance dependence. In addition, there was no family history of psychiatric illness, including substance use disorders among the healthy controls. All participants were evaluated by trained mental health professionals. Diagnosis and associated features were confirmed by a consultant psychiatrist of the OCD clinic (JCN).

Only right-handed subjects as ascertained by Edinburgh handedness inventory (Oldfield, 1971) were recruited for this study. None of the subjects had medical illnesses that could significantly influence CNS function or structure, significant neurologic disorder such as seizure disorder, cerebral palsy, or history suggestive of delayed developmental milestones and mental retardation, family history of hereditary neurologic disorders, comorbidity for DSM-IV psychoactive substance dependence, or lifetime history of head injury associated with any of the following: loss of consciousness longer than 10 min, seizures, neurological deficit, depressed skull fracture, surgical intervention, or central nervous system infection. The female subjects were neither pregnant nor were within the postpartum period.

2.3. EEG method

2.3.1. Flanker task

A modified version of the flanker task was displayed using STIM2 Neurobehavioral system, Neuroscan. The flanker task consisted of 500 trials (20 practice trials). Five arrows were presented on the screen and participants were instructed to respond to the direction of the central (target) arrow, with a right thumb press in a response device when the central arrow pointed towards the right direction and left thumb press when the central arrow pointed towards the left direction. The number of compatible (target and flanker stimuli pointing in same direction) and incompatible (target and flanker stimuli pointing in different direction) trials were same. The Flanker task was adapted from a previous study (Riesel et al., 2014). The task was run in eight blocks of 60 trials each. After each block of 60 trials, if the error rate was less than 10%, the participants were asked to respond faster during the next block. If the error rate was between 10–20%, the instruction for the next block was to respond both quicker and accurately. If error rate was more than 20%, the participants were asked to respond accurately in the next block. The total duration of the task was around 25 min.

2.3.2. EEG recording

EEG signals were recorded from the FCz, Cz, M1, and M2 (mastoid) electrodes using the Synamps RT system, Neuroscan, Compumedics EEG acquisition system. Impedance was kept below 15kΩ for all electrodes. The EEG activity was recorded with a sampling rate of 1000 Hz and filtered with a band pass filter of 0.01–100 Hz and a 50 Hz notch filter. Off-line, the data was filtered with 0.5–40 Hz bandpass filter and referenced to average of mastoid electrodes(Curry 7, Neuroscan). EEG recording was corrected for eye-movement artifacts using the covariate algorithm of Curry 7 software (Curry 7, Neuroscan). Response-locked epochs with duration of 800 msec, including a 200 msec pre-response interval were generated. Baseline correction was done from pre-stimulus 200 msec to 0 msec. Epochs containing voltage steps > 50 mV between consecutive data points were not included in the analysis and epochs having voltages above ± 100 μV were excluded from further analysis. Only subjects with atleast seven clean epochs for error trials were included in further analysis. Trials with response times less than 100 msec and greater than 700 msec were removed and the remaining epochs were averaged. Mean amplitude around peak measure 0–100 msec) post response was done for error responses- Error related negativity (ERN) and correct responses – correct response negativity (CRN).

2.4. Statistical analysis

Data was examined for normal distribution using the Shapiro-Wilk test. To examine the difference between the Error Related Negativity and Correct Response Negativity measures between the groups, independent samples *t*-test or Mann-Whitney *U* test was employed as appropriate. In addition, analysis of variance (ANOVA) with response correctness as a within factor was performed to examine the difference in ERN measures. To examine the relationship of ERN measures with demographic and illness severity measures, Spearman's correlation was used. P value < 0.05 was considered as the threshold for statistical significance.

3. Result

The two groups (OCD vs. Healthy controls) were comparable with respect to age (29.3 ± 5.9 vs. 29.0 ± 4.5 years; $t = 0.14$; $p = 0.89$) and sex distribution (male: female = 13:3 vs. 12:5; chi = 0.51; $p = 0.48$). Among the patients with OCD, the mean illness duration was 138.0 ± 112.7 months (median = 132 months) and the mean age of onset of OCD was 17.9 ± 8.7 years. The mean YBOCS obsession score, compulsion score and total scores were 13.9 ± 2.8, 13.7 ± 2.9 and 27.6 ± 5.0 respectively. The mean HDRS and the HARS scores were 11.4 ± 6.9 and 12.5 ± 6.7 respectively. The profile of OCD symptoms were as follows: fear of contamination ($N = 10$), aggressive obsessions ($N = 6$), sexual obsessions ($N = 7$), blasphemous obsessions ($N = 7$), pathological doubts ($N = 10$), need for symmetry ($N = 4$) and miscellaneous obsessions ($N = 4$).

The comparison of the flanker task and Error related negativity and Correct response negativity measures between OCD patients and healthy controls is depicted in Table 1. There was no significant difference in the number of correct responses and number of errors on the flanker task between the OCD patients and healthy controls. However, ERN amplitude corresponding to Cz and FCz were significantly greater in subjects with OCD compared to Healthy controls as shown in Figs. 1 and 2. ANOVA with response correctness as a within subject factor revealed a significantly greater ERN amplitude corresponding to the Cz