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Research report

Acute dosing of vortioxetine strengthens event-related brain activity associated with engagement of attention and cognitive functioning in rats

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ABSTRACT

Studies of the antidepressant vortioxetine have demonstrated beneficial effects on cognitive dysfunction associated with depression. To elucidate how vortioxetine modulates neuronal activity during cognitive processing we investigated the effects of vortioxetine (3 and 10 mg/kg) in rats performing an auditory oddball (deviant target) task. We investigated neuronal activity in target *vs* non-target tone responses in vehicle-treated animals using electroencephalographic (EEG) recordings. Furthermore, we characterized task performance and EEG changes in target tone responses of vortioxetine *vs* controls. Quantification of event-related potentials (ERPs) was supplemented by analyses of spectral power and inter-trial phase-locking. The assessed brain regions included prelimbic cortex, the hippocampus, and thalamus. As compared to correct rejection of non-target tones, correct target tone responses elicited increased EEG power in all regions. Additionally, neuronal synchronization was increased in vehicle-treated rats during both early and late ERP responses to target tones. This indicates a significant consistency of local phases across trials during high attentional load. During early sensory processing, vortioxetine increased both thalamic and frontal synchronized gamma band activity and EEG power in all brain regions measured. Finally, vortioxetine increased the amplitude of late hippocampal P3-like ERPs, the rodent correlate of the human P300 ERP. These findings suggest differential effects of vortioxetine during early sensory registration and late endogenous processing of auditory discrimination. Strengthened P3-like ERP response may relate to the pro-cognitive profile of vortioxetine in rodents. Further investigations are warranted to explore the mechanism by which vortioxetine increases network synchronization during attentive and cognitive processing.

1. Introduction

Development of drugs to treat cognitive dysfunction is challenged by high attrition rates of potential compounds and a lack of predictive models. Many preclinical tests have low predictive validity for efficacy in humans (Garner, 2014). Attended auditory oddball tasks have been suggested to have a broader translational potential (Grupe et al., 2014). In these tasks, both cognitive behavior and concurrent neuronal processing can be investigated. Deviant target (oddball) tones are presented among frequent irrelevant non-target tones while the animal presses a button only when target tones are detected (Grupe et al., 2014; Laursen et al., 2014).

Oddball tasks are optimized to evoke event-related potentials (ERPs) containing a late endogenous positive deflection called P300 or P3 (Polich and Corey-Bloom, 2005). When auditory stimuli are presented, subsequent evaluation of ERPs offers a unique opportunity to investigate time-locked neuronal oscillations during cognitive processes. The characteristics of the evoked neuronal activity are commonly demonstrated by traditional synchronous averaging in the time domain and subsequent quantification of the grand average ERP. However, spectral analyses with high resolution of time and frequency can be applied for more detailed

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investigation of the involvement of specific frequency bands (Richard et al., 2017; Roach and Mathalon, 2008).

The conspicuous waveform of ERPs evoked in oddball tasks may be divided into components defined by polarity, amplitude, and latency, and these components are commonly interpreted as functionally distinct stages related to the auditory response and subsequent cognitive processing. Early components (P1, N1, and P2) constitute the pre-attentional response and are believed to be involved in initial encoding and classification of stimuli (Crowley and Colrain, 2004; Swann et al., 2013). In humans, long-latency components such as N2 and the cognitive potential P3 are recognized as a brief negative deflection followed by a sustained positive shift around 300–400 ms in response to deviant stimuli (Siegel et al., 2003). N2 and particularly P3 comprise the attentional part of the ERP and are only elicited if the subjects allocate attention to the stimuli (Duncan et al., 2009; Tong et al., 2009).

It remains to be fully established if rodent and human ERPs are functionally and neurobiologically equivalent. Although rodent auditory potentials peak at shorter latency, the morphological characteristics of the deflections, i.e., the P1-N1-P2 complex, are comparable in rodents and humans during the sensory processing of auditory events (Siegel et al., 2003). Furthermore, rat P3-like ERPs may be pharmacologically disrupted, enhanced, or rescued (Grupe et al., 2014; Gurley et al., 2010; Laursen et al., 2014), consistent with effects seen in human studies (Callaway et al., 1991; Ray et al., 2012; Reeves et al., 1999). These observations have instigated current investigations of the utility of the rodent P3-like ERP as a biomarker for cognitive processing in humans.

The prevailing pharmacotherapy of major depressive disorder involves inhibition of the serotonin transporter (SERT), exemplified by selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors. Many studies support an important but highly complex role of the serotonergic system in regulation of cognitive processes (reviewed by Leiser et al., 2015). Thus, both inhibitory and excitatory serotonin receptors and the SERT are highly expressed on both excitatory pyramidal cells and inhibitory interneurons in prefrontal and sensory regions (Puig et al., 2004; Sari, 2004; Varnas et al., 2004). This supports accumulating evidence suggesting the critical involvement of serotonin receptors in attentional and cognitive processes and auditory discrimination (Ehlers et al., 1991; Enge et al., 2011; Hurley, 2006; Leiser et al., 2015; Westrich et al., 2015).

Empirical data from preclinical studies suggest that the net effect of a decreased or increased serotonin tone (e.g., through depletion of the serotonin precursor tryptophan or administration of an SSRI) is generally speaking 'cognition neutral' (Leiser et al., 2015). The clinical evidence is rather limited but tends to support this notion (Rosenblat et al., 2015). On the other hand, the antidepressant vortioxetine (SERT inhibitor, 5-HT_{1A} receptor agonist, 5-HT_{1B} receptor partial agonist, and 5-HT_3, 5-HT_7, and 5-HT_{1D} receptor antagonist (Bang-Andersen et al., 2011; Mørk et al., 2012)) has consistently shown pro-cognitive effects in rodent models (Bétry et al., 2015; du Jardin et al., 2014; Jensen et al., 2014; Wallace et al., 2014; Westrich et al., 2015) and beneficial effects on aspects of cognitive dysfunction in patients with depression (Katona et al., 2012; Rosenblat et al., 2015; McIntyre et al., 2014; Mahableshwarkar et al., 2015). Chronic vortioxetine administration induces robust enhancement in neurogenesis in the hippocampal dentate gyrus in rats and mice (Bétry et al., 2015; Guilloux et al., 2013). Additionally, electrophysiological recordings in rats suggest that vortioxetine strengthens neuronal activity within EEG frequency bands involved in cognitive functioning (Dale et al., 2014; Leiser et al., 2014). Furthermore, *in vivo* recordings of rat prefrontal cortical pyramidal cells showed that vortioxetine, but not the SSRI escitalopram, increased their firing rate, and this was most likely through 5-HT_3 receptor-mediated inhibition of gamma-aminobutyric acid (GABA) interneurons (Riga et al., 2015).

Based on these observations, we investigated vortioxetine's effects on behavioral performance and electrophysiological responses in cognitively engaged rats. We hypothesized that vortioxetine would strengthen the neuronal activity underlying the cognitive behavior during auditory change detection.

The study aims were: 1) to characterize neuronal activity in target *vs* non-target tone responses after vehicle administration and 2) to evaluate the underlying neuronal activity during cognitive behavior in vortioxetine-treated *vs* vehicle-treated rats. A two-tone auditory discrimination task was performed during simultaneous recording of local field potentials. The anatomical regions of interest were areas commonly related to sensory integration and mnemonic processes: the prelimbic region of the frontal cortex (PrL), the ventral cornu ammonis subdivision of the hippocampus (vCA1), and the mediodorsal region of thalamus. Behavioral assessment accompanied the electrophysiological characterization.

2. Results

2.1. Target versus non-target tone responses in vehicle-treated rats

Grand average waveforms of ERPs are presented in Fig. 1A–C. The amplitude of the P3-like potential was significantly higher in responses to target *vs* non-target tones in all brain regions investigated (thalamus: mean difference 0.0076 ± 0.015 mV, $t = 2.0$, $p = 0.03$; hippocampus: mean difference 0.014 ± 0.02 mV, $t = 2.1$, $p = 0.03$; PrL: mean difference 0.014 ± 0.019 mV, $t = 2.3$, $p = 0.02$). Peak amplitudes of P2 and N2 were significantly higher in target tone responses in hippocampus (P2: mean difference 0.058 ± 0.057 mV, $t = -3.7$, $p = 0.003$; N2: mean difference −0.032 ± 0.028 mV, $t = 4.0$, $p = 0.002$), while the N2 amplitude was significantly higher in thalamus (N2: mean difference −0.032 ± −0.019 mV, $t = -2.1$, $p = 0.02$) during target tone responses. The peak latencies of all ERP subcomponents were comparable in all investigated regions.

Spectral analyses revealed differential evoked EEG power in target and non-target tone responses (Fig. 1D). The difference between the responses is expressed in Fig. 1E. Here, the evoked power was increased in target tone responses at frequencies <40 Hz, ranging from ~0 to 225 ms after target stimuli for all electrodes. Additionally, target tone responses were characterized by solid increases in stimulus-evoked phase-locking within the early and late parts of the auditory response (Fig. 1F–G). In thalamus, the early response was characterized by increased phase-locking at frequencies >20 Hz in target tone responses, while phase-locking was observed primarily at frequencies <30 Hz in the hippocampus and PrL. Late responses were characterized by increased phase-locking of low frequency oscillations (<20 Hz) at all electrodes.

2.2. Effects of vortioxetine on target tone responses

The accuracy of behavioral responses was evaluated as percent lever presses to the tones (Fig. 2A–C). All treatment groups responded to target tones with ~90% accuracy and to non-target tones with ~80% accuracy. There was a significant difference between lever presses to the two tones within all treatment groups (vehicle: $t = 23.8$, $p < 0.001$; 3 mg/kg vortioxetine: $t = 25.6$, $p < 0.001$; 10 mg/kg vortioxetine: $Z = -3.8$, $p < 0.001$). Conversely, there was no difference between responses to target ($\chi^2 = 4.0$, $p = 0.13$) and non-target tones ($F_{(2,36)} = 2.6$, $p = 0.09$) between treatment groups.