Psychiatry Research: Neuroimaging 252 (2016) 10–18

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

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

Pharmacological modulation of pulvinar resting-state regional oscillations and network dynamics in major depression

Reza Tadayonnejad [a,*], Olusola Ajilore [a], Brian J. Mickey [b], Natania A. Crane [a], David T. Hsu [b], Anand Kumar [a], Jon.-Kar. Zubieta [b], Scott A. Langenecker [a]

[a] Department of Psychiatry, University of Illinois at Chicago, Chicago, IL, USA
[b] Department of Psychiatry, University of Michigan, Ann Arbor, MI, USA

ARTICLE INFO

Article history:
Received 16 December 2015
Received in revised form
15 March 2016
Accepted 26 April 2016
Available online 27 April 2016

ABSTRACT

The pulvinar, the largest thalamus nucleus, has rich anatomical connections with several different cortical and subcortical regions suggesting its important involvement in high-level cognitive and emotional functions. Unfortunately, pulvinar dysfunction in psychiatric disorders particularly major depression disorder has not been thoroughly examined to date. In this study we explored the alterations in the baseline regional and network activities of the pulvinar in MDD by applying spectral analysis of resting-state oscillatory activity, functional connectivity and directed (effective) connectivity on resting-state fMRI data acquired from 20 healthy controls and 19 participants with MDD. Furthermore, we tested how pharmacological treatment with duloxetine can modulate the measured local and network variables in ten participants who completed treatment. Our results revealed a frequency-band dependent modulation of power spectrum characteristics of pulvinar regional oscillatory activity. At the network level, we found MDD is associated with aberrant causal interactions between pulvinar and several systems including default-mode and posterior insular networks. It was also shown that duloxetine treatment can correct or overcompensate the pathologic network behavior of the pulvinar. In conclusion, we suggest that pulvinar regional baseline oscillatory activity and its resting-state network dynamics are compromised in MDD and can be modulated therapeutically by pharmacological treatment.

1. Introduction

The pulvinar, located in the posterior part of the thalamus, is the largest primate thalamic nucleus. The pulvinar has extensive bidirectional connections with temporal, parietal, cingulate, frontal and insular cortices reported in primate tracing and human diffusion tensor imaging (DTI) studies (Jones and Burton, 1976; Kumar et al., 2014; Shipp, 2003). Pharmacological imaging studies of thalamic neurotransmission have detected the presence of active serotonergic and noradrenergic but little to no dopaminergic activity in the pulvinar part of thalamus (Oke et al., 1997; Takano et al., 2008).

The pulvinar was once considered a simple "relay center" for information transmission between thalamus and cortex (Pessoa and Adolphs, 2010). That simplistic model of pulvinar function has been revised by recent evidence showing an intricate computational role of the pulvinar in modulating cortical synchrony needed for perceptual attention and emotional processing (Padmala et al., 2010; Pessoa and Adolphs, 2010; Saalmann et al., 2012).

Pulvinar anatomical and physiological abnormalities have also been found to be involved in the pathophysiology of different neuropsychiatric disorders like visual neglect syndrome, attentional deficits, anxiety disorders and attention deficit hyperactivity disorder (ADHD) (Arend et al., 2008; Ipser et al., 2013; Ivanov et al., 2010; Snow et al., 2009). In addition, results of a recent meta-analysis of resting-state PET and SPECT studies in MDD found a significant increase in pulvinar baseline activity in participants with MDD suggesting pulvinar hyperactivity as a potential mechanism of "heightened negative stimuli processing and awareness" (Hamilton et al., 2012). Prior studies also show abnormal functional connectivity of thalamic regions, if not the pulvinar specifically, in MDD (Greicius et al., 2007). Furthermore, μ-opioid availability in the pulvinar was predictive of degree of treatment response in MDD (Kennedy et al., 2006). Abnormalities in serotonin transporter system and pulvinar volume size via neuron counts were also reported in a postmortem study of individuals with history of MDD (Young et al., 2007).

In the last decade, resting-state fMRI (rsfMRI) method has been used extensively to investigate regional and network dysfunction

* Correspondence to: The Institute for Juvenile Research (room#216), 1747 West Roosevelt Road, Chicago, IL 60608, USA.
E-mail address: rtadayon@psych.uic.edu (R. Tadayonnejad).

http://dx.doi.org/10.1016/j.pscychresns.2016.04.013
0925-4927/

in neuropsychiatric disorders including major depressive disorder (Biswal et al., 1995; Fox and Raichle, 2007). Spectral analysis based approaches of Amplitude of Low-Frequency Fluctuation (ALFF) or Fractional ALFF (fALFF) are applied for measuring characteristics of regional activity in different brain regions in normal and pathologic conditions (Zang et al., 2007; Zou et al., 2008). Using ALFF/fALFF methods, several studies have shown alterations in resting state baseline activity in several cortical (frontal, temporal and cingulate) and subcortical (thalamus, striatum) regions (Lai and Wu, 2015; Tadayonnejad et al., 2014). More than looking at resting-state regional activity of brain, rsfMRI data has been used to explore network dysfunction in depression. For that purpose, two main approaches of functional connectivity (FC) and effective connectivity (EC) are practiced to measure interregional correlation (synchronicity) or causal influence between interacting brain regions respectively (Friston, 2011). Findings of a recent meta-analysis of FC studies in major depressive disorder showed the frontoparietal network hypoconnectivity, hyperconnectivity within the default mode network, believed to be involved in internally oriented and self-referential thought processing, and hypoconnectivity in neural networks mediating top-down emotion regulation in subjects with depression compared to healthy controls (Kaiser et al., 2015). EC studies in depression have also found impairment in causal dynamics behavior of areas involve in neurocircuitry of depression particularly medial frontal and anterior cingulate cortex (Feng et al., 2016; Hamilton et al., 2011).

Despite intriguing evidence for a role of the pulvinar nucleus in the pathology and expression of MDD, there are still many important gaps in our knowledge. By applying above-mentioned fALFF, FC and EC analysis methods on resting-state fMRI data, we want to explore pulvinar regional and network dysfunction in depression. We hypothesize that MDD is associated with alterations in pulvinar regional resting-state oscillatory activity and also its network dynamics. Furthermore, we hypothesize that pharmacological treatment with the serotonin-norepinephrine reuptake inhibitor duloxetin can change (correct or overcompensate) MDD related changes in regional activity and network behavior of pulvinar.

2. Methods

2.1. Participants

Twenty-four subjects with diagnosis of major depressive disorder and 26 sex- and age-matched health control subjects were recruited in this study. Nineteen MDD who completed the first part of the study and had data at free of movement and distortion artifacts were included in the analyses and reported in this paper, along with 20 healthy control subjects with usable data at baseline. Healthy control subjects were only studied at baseline. Clinical assessment was conducted using the structured clinical interview for DSM-IV and the Hamilton Rating Scales for Depression and Anxiety. BJM or JKZ provided treatment for participants through the Translational Neuroimaging Laboratory at the University of Michigan Medical Center, supported by services and clinic space provided by the Michigan Clinical Research Unit. Prior to enrollment in the study, MDD participants were unmedicated and had been medication-free for at least 90 days for any SSRIs or SNRIs and for at least 30 days for all other medications (including birth control) to eliminate medication effects on functional neural activation. Individuals who smoked cigarettes, met criteria for alcohol abuse, or had used any illegal drugs in the past 2 years were excluded. All MDD participants underwent fMRI and completed several measures including the Hamilton Depression Rating Scale (HDRS) at baseline. Ten of nineteen MDD participants completed open-label treatment with duloxetine for 10 weeks with second scanning and psychological assessment after treatment. Participants were given 30 mg during weeks 1–2 and then 60 mg during weeks 3–6. If participants' symptoms had not improved by at least 50%, participants' dose was titrated up to 90 mg during weeks 7–8 and if symptoms had still not improved by at least 50%, their dose was titrated up to 120 mg during weeks 9–10, and then either continued on a 60 mg dose or were given 90 mg if symptoms had not improved by at least 50%. Repeat fMRI and HDRS measurements took place upon completion of treatment.

2.2. Data acquisition

Whole brain, eyes-open resting state scans were performed with a 3.0 T GE Signa scanner (Milwaukee, Wisconsin) over 8 min using a standard ratio frequency coil and $T2^*$-weighted pulse sequence with a gradient-echo axial forward-reverse spiral sequence at UM (2). The following parameters were used: echo time = 3.4 ms, TR = 2 sec, degree flip = 27, field of view = 22 cm, matrix size = 64×64, slice thickness = 5 mm, slices = 30. High-resolution anatomical T1 scans were obtained for spatial normalization. During scanning, participants were asked to look at a fixation cross on the display and the importance of staying still was conveyed to each participant.

2.3. fMRI preprocessing

All preprocessing were conducted using statistical parametric mapping software (SPM8, http//www.fil.ion.uvl.ac.uk/spm). The first 10 volumes of the functional images were discarded for obtaining signal equilibrium and allowing participants adaptation to scanning noise. The artifact detection tool (ART: http://www.nitrc.org/projects/artifact_detect) was used to measure motion artifacts in all subjects. None of the subjects used in this study had more than 1 mm maximum displacement in x, y or z axis or 1 angular motion during fMRI scanning. Furthermore, there was no significant difference in composite motion between groups (HC: 0.13 ± 0.01; pre-treatment MDD: 0.16 ± 0.03; post treatment MDD: 0.17 ± 0.04). Raw EPI images were subsequently realigned, coregistered, normalized, and smoothed with a smoothing kernel of 8 mm before analyses. Confound effects from motion artifact, white matter, and CSF were regressed out of the signal. We did not regress out whole-brain noise effect. Finally, BOLD signal data were passed through two band-pass filters (lower frequency band (LF): 0.01–0.1 Hz and higher frequency band (HF): 0.1–0.25 Hz) for further fALFF and functional connectivity analyses.

2.4. Power spectrum distribution analysis

Lower and higher frequency bands power spectrum distribution were calculated in terms of Lower and Higher Frequency fractional Amplitude of Low-Frequency Fluctuation (LF/HF fALFF) values. fALFF analyses were performed using Resting-State fMRI Data Analysis Toolkit (REST, http://www.rest.restfmri.net). For each voxel, the filtered time series was transformed to the frequency domain using a fast Fourier transformation (FFT) analysis, and the power spectrum was then measured. The average square root of power in the 0.01–0.1 Hz (LF) or 0.1– 0.25 Hz (HF) bands was calculated. Then, the average square root of power in the 0.01–0.1 Hz or 0.1–0.25 Hz bands for each voxel was normalized by total power across all available frequencies for that voxel (LF-fALFF and HF-fALFF). We applied a brain mask on subject-level voxel-wise fALFF maps for removing non-brain tissues. Finally, all fALFF maps were standardized into subject-level Z-score maps for improving statistical analyses and test-retest reliability (Chen et al., 2013; Zuo et al., 2010).