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Higher order thalamic nuclei resting network connectivity in early schizophrenia and major depressive disorder

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ABSTRACT

The pulvinar and the mediodorsal (MDN) nuclei of the thalamus are higher order nuclei which have been implicated in directed effort and corollary discharge systems. We used seed-based resting fMRI to examine functional connectivity to bilateral pulvinar and MDN in 24 schizophrenic patients (SZ), 24 major depressive disorder patients (MDD), and 24 age-matched healthy controls. SZ had less connectivity than controls between the left pulvinar and precuneus, left ventral-lateral prefrontal cortex (vlPFC), and superior and medial-frontal regions, between the right pulvinar and right frontal pole, and greater connectivity between the right MDN and left dorsolateral prefrontal cortex (dlPFC). SZ had less connectivity than MDD between the left pulvinar and ventral anterior cingulate (vACC), left vlPFC, anterior insula, posterior cingulate cortex (PCC), and right hippocampus, between the right pulvinar and right PCC, and between the right MDN and right dorsal anterior cingulate (dACC). This is the first study to measure the functional connectivity to the higher order nuclei of the thalamus in both SZ and MDD. We observed less connectivity in SZ than MDD between pulvinar and emotional encoding regions, a directed effort region, and a region involved in representation and salience, and between MDN and a directed effort region.

1. Introduction

The thalamus is a hub of cortical-subcortical connections and a regulator of cortical activity (Giraldo-Chica and Woodward, 2017). Although historically viewed only as a relay station between sensory organs and the cortex, the thalamus likely plays a central role in cortical functioning (Sherman, 2016). With the evolutionary expansion of the cortex in primates, there is a reason to believe that the thalamus underwent a parallel enlargement to accommodate increased complexity in cortical connectivity (Bridge et al., 2016).

Abnormal thalamic structure and functional connectivity have been implicated in the neuropathology of schizophrenia and mood disorders (Cerullo et al., 2009; Giraldo-Chica and Woodward, 2017; Glahn et al., 2008; Pergola et al., 2015; Sim et al., 2006; Woodward and Heckers, 2016). Recent studies have examined distinct thalamic nuclei to investigate specific anomalous thalamocortical circuits in psychosis (Giraldo-Chica and Woodward, 2017; Woodward and Heckers, 2016). The pulvinar nuclei and mediodorsal nucleus (MDN) are two higher order nuclei of the thalamus that primarily receive input from the cortex (Giraldo-Chica and Woodward, 2017), and they have both been shown to have reduced volume in patients with schizophrenia compared to healthy volunteers (Byne et al., 2009; Kemether et al., 2003) and have both been found to show anomalies in post-mortem studies (Byne et al., 2002; Dorph-Petersen and Lewis, 2017; Pakkenberg, 1990, 1992; Popken et al., 2000; Young et al., 2000).

The pulvinar is a central forebrain hub with a critical role in vision

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and cognition with reciprocal connections to the prefrontal cortex and parietal and temporal lobes (Kemether et al., 2003). It has been proposed that the pulvinar nuclei may contribute to unique human adaptions related to tool use and language and its expansion in humans may have led to a wider range of cognitive abilities than in other primates (Bridge et al., 2016). The human pulvinar nuclei are proposed to have a role in focused attention by filtering distracting stimuli (Strumpf et al., 2013), which is known to be deficient in schizophrenia.

The MDN projects to the prefrontal cortex (dlPFC) (Bridge et al., 2016; Welsh et al., 2010), which plays a central role in the networks affected in schizophrenia and mood disorders and is known to have functional and structural deficits in schizophrenia (SZ) and mood disorders (Williamson and Allman, 2012). It has also been proposed that driver inputs from the cortex to higher order regions of the thalamus may act as efference copies, also known as corollary discharges, for information relayed to the cortex (Sherman, 2016). Corollary discharges allow for the detection of unexpected stimuli, and there is evidence of deficits in corollary discharge in schizophrenia (Feinberg and Guazzelli, 1999; Ford et al., 2014; Pynn and DeSouza, 2013).

A recent paper by Woodward and Heckers (2016) used resting functional magnetic resonance imaging (fMRI) to investigate the connectivity between thalamic subregions and the cortex in early and chronic patients with psychotic disorders versus healthy controls. They reported reduced thalamic connectivity to the dlPFC, medial prefrontal cortex (mPFC), and the executive control network in subjects with psychosis (Woodward and Heckers, 2016). Our previous paper (Penner et al., 2016) found decreased connectivity between basal ganglia-thalamocortical regions and the mPFC in schizophrenia compared to major depressive disorder (MDD), decreased connectivity between mPFC and dorsal anterior cingulate cortex (ACC) and other directed effort regions in schizophrenia compared to controls. Also, we identified decreased connectivity between mPFC and ventral prefrontal emotional encoding regions in MDD compared to controls. However, our previous paper reported on seed-based connectivity to the mPFC and did not directly measure connectivity to the higher order thalamic nuclei.

The present study aims to measure the functional connectivity to higher order nuclei of the thalamus, instead of their projections, in patients early in illness. To our knowledge this is the first study directly investigating the higher order thalamic nuclei using seed-based fMRI in both schizophrenia and MDD, along with healthy controls. The objective was to determine if functional connectivity between higher order thalamic nuclei, pulvinar and MDN, and the cortex is abnormal in early schizophrenia and early MDD and whether thalamic connectivity can help differentiate the two illnesses. We hypothesized that there would be deficient connectivity to regions involved in directed effort in schizophrenia and deficient connectivity to emotional encoding network regions in MDD.

2. Methods

2.1. Participants

Twenty-four patients with schizophrenia (SZ) and 24 patients with major depressive disorder (MDD), both early in illness, were recruited along with 24 healthy controls (HC) from the community and through the Prevention and Early Intervention in Psychosis and First Episode Mood and Anxiety Programs in London, Ontario, Canada, and were matched for age, handedness, and parental education level. A consensus diagnosis was obtained for all patients using the Structural Clinical Interview for DSM-IV (SCID) (First et al., 1997) by an experienced rater (B.S.) and psychiatrist (P.C.W.), and to exclude psychiatric diagnoses in healthy controls. The Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984b) and the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1984a) in patients with schizophrenia and the Montgomery-Asberg Depression Scale (Montgomery and Asberg, 1979) in patients with MDD were used to rate symptom severity immediately prior to the fMRI scan. Exclusionary criteria for patients and controls included a history of drug or alcohol abuse or dependence in the previous year, mental retardation, hypertension, diabetes, hepatic/renal insufficiency or neurological conditions. Additionally, controls with a first- or second-degree relative with a known psychiatric disorder were excluded. This study protocol was approved by the research ethics board at the University of Western Ontario.

2.2. Magnetic resonance imaging data acquisition

All imaging data was acquired on a 3 T magnetic resonance imaging (MRI) scanner (Siemens Tim Trio, Erlangen, Germany) located at the Centre for Functional and Metabolic Mapping (CFMM; Robarts Research Institute, University of Western Ontario), equipped with a 32-channel head coil. Structural anatomical images (T1-weighted MPRAGE, whole-brain coverage, 1 mm isotropic resolution) were acquired for spatial normalization of the functional data and to measure potential volumetric differences between subject groups that could have influenced our functional connectivity results. The resting functional scan was acquired over 10 min and covered the entire brain with 2 mm isotropic resolution (2D T2*-weighted gradient-echo, echo-planar, TR = 3 s, TE = 20 ms, 128 × 128 matrix size, 60 slices, 3 initial discarded volumes, 200 functional volumes, parallel to the AC-PC plane). During the resting functional scan, participants were instructed to keep their eyes closed and let their minds wander, and to not to fall asleep; all participants reported that they did not fall asleep.

2.3. Seed-based resting functional connectivity analysis

Standard preprocessing was done on the resting functional images. To correct for motion, each image volume within a scan was aligned to the first volume based on 6 movement parameters (translation in x, y, z and rotation in yaw, pitch, roll; INRIAlign, http://www-sop.inria.fr/epidaure/Collaborations/IRMf/INRIAlign). The resting functional images were then normalized into the standard Montreal Neurological Institute space using the corresponding T1-weighted anatomical images, and smoothed with a 6 mm full width at half-maximum 3D Gaussian kernel (SPM8, http://www.fil.ion.ucl.ac.uk/spm). Mean global image intensity outliers and excessive movement were detected using ARtifact detection Tools (ART, http://www.nitrc.org/projects/art), and a multiple regressor file was generated for each participant containing the 6 realignment parameters and a seventh regressor for flagged outliers. Participants with greater than 2 flags (> 2 mm movement) were removed from the analysis, 2 patients with SZ were excluded.

Connectivity between higher order thalamic nuclei and the rest of the brain was examined with seed-based connectivity analyses, as previously detailed (Bluhm et al., 2009), using SPM8. The resting functional data were band-passed filtered (0.012–0.1 Hz) and the average BOLD time series were extracted from four 3 mm radius spherical seed regions centered in; left pulvinar nuclei (− 12,− 27,5; MNI coordinates), right pulvinar nuclei (12,− 27,5; MNI coordinates), left MDN (− 6,− 7,8; MNI coordinates), and right MDN (6,− 7,8; MNI coordinates); seed center MNI coordinates carefully identified by a neuroanatomist (N.R.). The extracted time series from each seed region were then entered into a first-level, or within-participant, general linear model analysis as regressors of interest to generate functional connectivity maps for each seed region for each participant. The multiple regressor file containing the 6 realignment parameters and flagged outliers were entered into the general linear model as regressors of no interest to mitigate residual movement and artifacts. The positive correlation t-maps for each participant, which represent the correlation strength of each voxel to the seed region, were carried forward to the group-wise analysis.

Within-group connectivity patterns [ANCOVA, n = 72, df = 67, family-wise error (FWE) corrected at $p < 0.001$] and between-group

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