



Disrupted modulation of thalamus activation and thalamocortical connectivity during dual task performance in schizophrenia

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ABSTRACT

Despite considerable evidence showing thalamus anatomy and connectivity abnormalities in schizophrenia, how these abnormalities are reflected in thalamus function during cognition is relatively understudied. Modulation of thalamic connectivity with the prefrontal cortex (PFC) is required for higher-order cognitive processes, which are often impaired in schizophrenia. To address this gap, we investigated how thalamus function and thalamus-PFC connectivity under different levels of cognitive demand may be disrupted in schizophrenia. Participants underwent fMRI scanning while performing an event-related two-alternative forced choice task under Single and Dual task conditions. In the Single task condition, participants responded either to a visual cue with a well-learned motor response, or an audio cue with a well-learned vocal response. In the Dual task condition, participants performed both tasks. Thalamic connectivity with task relevant regions of the PFC for each condition was measured using beta-series correlation. Individuals with schizophrenia demonstrated less modulation of both mediodorsal thalamus activation and thalamus-PFC connectivity with increased cognitive demand. In contrast, their ability to modulate PFC function during task performance was maintained. These results suggest that the pathophysiology of cognitive impairment in schizophrenia is associated with thalamus-PFC circuitry and suggests that the thalamus, along with the PFC, should be a focus of investigation.

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1. Introduction

Abnormal function of the thalamus and thalamic connectivity with the prefrontal cortex (PFC) is thought to be fundamental to cognitive impairment in schizophrenia (Andreasen, 1997). There is considerable evidence that the structure and connectivity of the thalamus is abnormal in schizophrenia (Giraldo-Chica et al., 2018; Pergola et al., 2017; van Erp et al., 2016). However, few studies have investigated thalamic dysfunction during cognitive tasks. Several early studies found thalamic hypofunction in schizophrenia while performing verbal and spatial working memory tasks (Andrews et al., 2006; Camchong et al., 2006; Choi et al., 2012; Schlösser et al., 2008; Schneider et al., 2007), attention tasks (Salgado-Pineda et al., 2004), prepulse inhibition (Hazlett et al., 2008; Kumari et al., 2007) and oddball tasks (Gur et al., 2007; Kiehl and Liddle, 2001; Laurens et al., 2005), though other studies have found thalamus hyperfunction while performing sensory gating tasks (Tregellas et al., 2007; Tregellas et al., 2009), word encoding tasks (Ragland et al., 2005) and target detection (Bor et al., 2011). These

studies typically examined thalamic function during a cognitive task compared to baseline, rather than modulation by cognitive demand.

Thalamic hypofunction was more prominent during tasks with higher cognitive demand, such as tasks requiring mental updating or manipulation. In a modified Sternberg task, thalamic hypofunction was observed when manipulation of maintained information was required, but not while passively maintaining information (Schlösser et al., 2008). A recent study found thalamic hypofunction during encoding and maintenance, but not retrieval of spatial information (Choi et al., 2012). In contrast, thalamic hyperfunction was observed during sensory tasks (Tregellas et al., 2007, 2009). These thalamic findings are consistent with PFC dysfunction in schizophrenia, where a shifted inverted-U shaped curve is observed in patients, such that PFC hyperfunction is observed in high performing patients, or during easier tasks, and PFC hypofunction is observed in low performing patients, or during difficult tasks (Callicott et al., 2000; Karlsgodt et al., 2009; Manoach, 2003). In this study, we investigated modulation of thalamic function by cognitive demand in schizophrenia.

The thalamus is composed of multiple nuclei, with differentiable structure, function and connectivity patterns (Jones, 2007). Two thalamic nuclei have been particularly implicated during cognitive function; the mediodorsal nucleus (MD) and pulvinar (PUL). The MD has prominent anatomical connectivity with the PFC, and is central to

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various cognitive processes including working memory, attention and adaptive decision making (see Mitchell, 2015; Ouhaz et al., 2018 for reviews). The PUL shows extensive connectivity with the posterior parietal cortex and is implicated in visual attention processes (see Bridge et al., 2016 for review). Few functional studies of thalamic function in schizophrenia have investigated different regions of the thalamus during cognitive tasks. One study parcellated the thalamus into 7 regions of interest (ROIs) and investigated differential thalamic function of these regions during a visual working memory, intentional encoding and recognition tasks. This study found task-related thalamic hypofunction in the anterior and MD thalamus, but not similar changes in the PUL (Andrews et al., 2006).

In recent years, there has been increasing evidence of reduced thalamus-PFC structural and functional connectivity at rest in schizophrenia (Anticevic et al., 2013, 2014; Klingner et al., 2014; Skåtun et al., 2017; Wang et al., 2015; Welsh et al., 2010; Woodward and Heckers, 2016; Woodward et al., 2012; see Giraldo-Chica and Woodward, 2017 for review). In contrast, few studies have investigated task related connectivity changes in schizophrenia, though these studies have reported increased connectivity between the thalamus and PFC during verbal working memory (Schlösser et al., 2003; Wagner et al., 2013). Both of these studies investigated the effect of task compared to baseline, and differences in methods used to calculate connectivity make it difficult to reconcile resting state related reduced and task related increased thalamus-PFC connectivity.

The present study used a dual task paradigm requiring participants to perform either one two-alternative forced choice task or two tasks simultaneously to investigate modulation of thalamic function and connectivity by cognitive demand in individuals with schizophrenia compared to healthy individuals. We examined activation and connectivity from the MD, PUL and the ventrolateral thalamus (VL), a thalamic region that is part of the striato-thalamo-frontal network involved in motor function (Haber and Calzavara, 2009; Haber and McFarland, 2001). Importantly, we investigated thalamus-PFC connectivity modulation by different levels of cognitive demand in the same task, allowing us to use the same method for calculating connectivity. We hypothesized that patients would show reduced modulation of PFC and thalamus activation, and thalamus-PFC connectivity by cognitive demand.

2. Method

2.1. Participants

Twenty-two patients with schizophrenia and 24 healthy individuals matched for age, gender, ethnicity and parental education participated in this study. 6 subjects (4 healthy; 2 schizophrenia) were excluded for incomplete data and one healthy individual was removed for excessive head motion. Thus, the final sample included 20 schizophrenia patients and 19 healthy individuals. Demographics for subjects included in the analyses are presented in Table 1. Schizophrenia participants were recruited from inpatient and outpatient services at the Vanderbilt Psychiatric Hospital in Nashville, Tennessee, and healthy participants were recruited from Nashville and the surrounding area through advertisement and word-of-mouth. Our schizophrenia sample consisted of 17 outpatients and 2 inpatients (data from 1 participant was not available). One patient was unmedicated and 2 were not receiving any antipsychotic medications. This study was approved by the Vanderbilt University Institutional Review Board and all participants provided written informed consent prior to participating in this study. All participants were administered the Structured Clinical Interview for Diagnosing DSM-IV Disorders (SCID: First et al., 1996) to confirm diagnosis in patients and rule out current or past psychiatric illness in control subjects. Clinical symptoms in patients were quantified with the Positive and Negative Syndrome Scale (PANSS: Kay et al., 1987). Premorbid IQ was estimated using the Wechsler Test of Adult Reading (WTAR:

Table 1
Sample demographics.

Variable	CON		SCZ		Statistics		
	n = 19		n = 20		t/x ²	df	p
Sex (M:F)	8:11		10:10		0.24	37	0.621
Ethnicity (W:AA)	14:5		12:8		0.82	37	0.365
Handedness (L:R:A)	3:15:1		2:17:1		0.30	37	0.861
Smoking (Y:N)	3:16		7:13		1.89	37	0.170
Variable	Mean		SD		Statistics		
					t/x ²	df	p
Age	41.05	8.8	40.45	11.9	0.18	37	0.858
Education	16.42	2.1	13.80	2.3	3.72	37	<0.001
Maternal education	12.74	2.2	13.16	3.3	−0.47	36	0.642
Paternal education	13.84	3.3	13.16	4.1	0.57	36	0.573
WTAR	109.32	11.3	102.70	14.0	1.63	37	0.111
PANSS positive	–	–	13.8	6.1	–	–	–
PANSS negative	–	–	14.7	5.6	–	–	–
PANSS general	–	–	26.9	7.8	–	–	–
Age of onset	–	–	22.2	5.6	–	–	–
CPZ equivalent	–	–	387	262.3	–	–	–

Abbreviations: CON = Healthy Controls; SCZ = Schizophrenia Spectrum Disorder; AA = African American; A = Ambidextrous; CPZ = Chlorpromazine; df = Degrees of Freedom; F = Female; L = Left; M = Male; N = no; PANSS = Positive and Negative Syndrome Scale; R = Right; W = White; WTAR = Wechsler Test of Adult Reading; Y = yes.

Wechsler, 2001). Exclusion criteria included an estimated premorbid IQ of <70, age <18 or >60, presence of a systemic medical illness (i.e. diabetes, cardiovascular or central nervous system disorder that would affect study participation), history of significant head trauma, reported pregnancy or lactation, history of substance abuse/dependence (3-months in patients; lifetime in controls), psychotropic drug use (in healthy individuals), and any MRI contraindications (e.g. metal implants, claustrophobia).

2.2. Task

On each trial, participants performed either a visuo-motor task where a visual cue was mapped to a motor response, or an audio-vocal task where an audio cue was mapped to a vocal response (Single task condition), or both tasks with a 0 ms stimulus onset asynchrony (Dual task condition). Both visuo-motor and audio-vocal tasks were two-alternative forced choice tasks, mapping two stimuli to two responses. The visual stimuli were two greyscale male faces controlled for skin tone, hair color, neutral facial expression and hairline on a grey background. Participants responded to each face by pressing a button with either their right index or middle finger. The audio-vocal task consisted of two easily discriminable sounds (a complex tone and an edited natural sound) used previously in (Dux et al., 2006; Dux et al., 2009), each paired with a “Tay” or a “Koo” vocal response. On Single trials, one visual or auditory stimulus was presented for 200 ms, on Dual trials, both the visual and auditory stimuli were presented simultaneously. All trials were preceded by a 200 ms warning fixation and followed by a 12,000 ms inter-trial interval (see Fig. 1A for schematic). Participants completed a total of 5 runs while undergoing fMRI scanning with each run consisting of 12 Single (6 visuo-motor and 6 audio-vocal) and 12 Dual trials.

2.3. Data acquisition

Imaging data were collected on a 3T Philips Intera Achieva scanner located at the Vanderbilt University Institute of Imaging Science. High resolution T1 structural scans were collected with a 4.5 min 3D T1 fast field echo sequence (170 slices, TR/TE = 8.9/4.6, FOV = 256 × 256 × 170 mm, matrix = 256 × 256 × 170, flip angle = 8°). Echo-planar imaging functional scans were collected while participants performed the behavioral task (38 slices, TR/TE = 2000/25 ms, FOV = 240 × 240 mm,

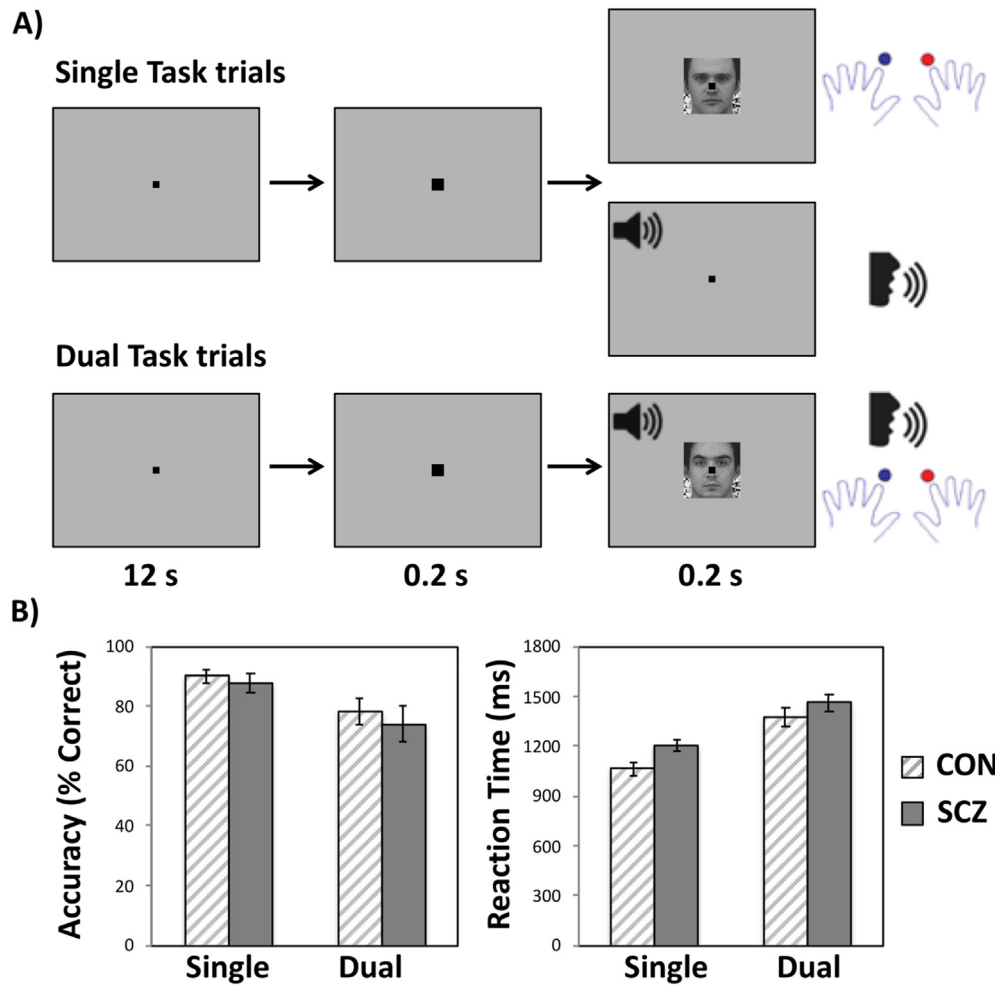


Fig. 1. A) Task schematic. For Single trials, participants responded to one of two images with a learned motor response or one of two audio tones with a learned vocal response, on Dual trials, both visual and audio cues were presented simultaneously and participants were requested to perform both responses. B) Behavioral performance. Single condition accuracy ranged from 70 to 100% for CON and 60 to 100% for SCZ. Dual condition accuracy ranged from 42 to 100% for CON and from 23 to 100% for SCZ. No significant group differences were found for either accuracy or reaction time. Abbreviations CON = Healthy control group; SCZ = Schizophrenia group.

matrix = 80×80 , slice thickness = 3 mm with 0.3 mm gap, flip angle = 90° , volumes = 203).

2.4. Data analyses

Neuroimaging preprocessing and subsequent analyses were carried out using SPM12 (version 7219) in Matlab (R2017b; MathWorks, USA). T1 structural images were skull stripped then segmented into grey and white matter tissue classes and normalized to MNI space using the CAT12 computational anatomy toolbox for SPM with default settings. Functional data underwent slice timing correction, motion correction followed by co-registration to the grey matter tissue segmentation. Deformation parameters from the structural normalization were then applied to all functional images, which were then smoothed with a 6 mm Gaussian kernel. For each subject, runs with motion larger than 3 mm in the x, y or z dimensions relative to the first volume in each run were excluded from further analysis. A total of 12 runs were excluded for excessive motion, with no subject having >2 of their 5 runs removed. A General Linear Model (GLM) was created for each subject with regressors defined separately for correct and incorrect Single and Dual trial onsets, convolved to a canonical hemodynamic response function. In addition, the model included covariates of no interest to account for the effect of 6 motion parameters (x, y, z, translation and roll, yaw and pitch). Vocal artifacts are limited to the first couple of seconds of responding and have limited effect on later hemodynamic response

(Birn et al., 2004). For each individual, estimated parameters of the regressors (beta weights) were calculated for each voxel using the GLM and were used in *t*-tests to assess the main effect of correct Dual > Single trials. Within group analyses were conducted separately for healthy and schizophrenia groups using subject level Dual > Single contrast images. Between group analyses were investigated for the Dual > Single contrast images from each individual using subject as a random effect. This analysis identifies regions that show a condition by group interaction. As we were interested in how the two groups differ in task relevant brain regions, whole brain group comparisons were masked for the Dual > Single contrast, collapsed across all subjects (thresholded at $p < 0.05$, uncorrected). For all masked analyses, we used small volume correction (SVC) to define cluster level significance. All contrasts used a voxel wise threshold of $p < 0.005$ to detect cluster level significance.

2.5. Region-of-interest analysis: PFC and thalamus

To further investigate PFC activation and thalamus-PFC connectivity, we defined 4 PFC regions of interest (ROIs) based on task activations. First, a prefrontal cortex mask was created using the frontal pole, superior frontal gyrus, middle frontal gyrus, inferior frontal gyrus pars triangularis and pars opercularis ROIs from the Harvard-Oxford cortical atlas (Desikan et al., 2006; <https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases>). All significant clusters in the Dual > Single contrast (collapsed across all subjects, $p < 0.05$, FDR_{SVC}) falling within this PFC mask were extracted. A

total of 4 ROIs were defined this way. They included the midline (pre) supplementary motor area (pre-SMA/SMA; $-4, 10, 56$; 357 voxels), left frontal eye fields (FEF; $-32, 0, 52$; 367 voxels), right lateral PFC (LPFC; $42, 10, 24$; 402 voxels) and the left LPFC ($40, 15, 22$; 97 voxels). For the all PFC ROI analyses, reported *p*-values were adjusted for Bonferroni corrected values based on 4 tests conducted.

For the thalamus, the voxel-wise between groups analysis was masked with a bilateral thalamus mask composed of the left and right thalamus from the Harvard-Oxford atlas. To further investigate activation patterns across different thalamic regions, we used the Morel atlas (Morel et al., 1997; Niemann et al., 2000) to define 3 thalamic regions covering the mediodorsal nucleus (MD; 236 voxels), the pulvinar (PUL; 543 voxels) and the ventrolateral nucleus (VL; 361 voxels). These 4 thalamus ROIs are presented in Supplementary Fig. 1. To correct for multiple thalamic regions, we report Bonferroni corrected *p*-values based on 3 tests conducted.

To ensure that these effects were not driven by differences in performance, a secondary set of analyses including only high performing subjects was also conducted (see Supplementary Table 3).

2.6. Beta-series connectivity

Task connectivity was conducted using the beta-series correlation analysis method (Rissman et al., 2004). Beta-series connectivity refers to a method of examining task connectivity by isolating a brain region's response to an event in a task (e.g. cue presentation) and then characterizing the covariance between task response in other brain regions, separately for each condition of interest. Beta-series differs from the more conventional psychophysiological interactions (PPI) method for investigating task connectivity in that power is derived from the number of trials/events presented, rather than based on time course correlations. In designs with many trials (>30) and short events, beta-series provides superior power to detect connectivity than PPI (Cisler et al., 2014). We constructed a GLM model including a regressor per trial to compute a separate parameter estimate (beta value) for each trial, resulting in 120 covariates of interest entered into the GLM (60 Single and 60 Dual trials). The GLM also included covariates of no interest to model the effects of shifting signal levels across runs and 6 motion parameters. This GLM resulted in a unique set of 120 beta values for each voxel in the brain. Beta values from correct trials were sorted into Single and Dual 'beta series' for each voxel in the brain. The task-based thalamus region from the between groups comparison of the Dual > Single contrast was used as a seed. Connectivity between this thalamus seed and each PFC ROI was calculated for the Dual and Single conditions by correlating their respective beta series. Additional analyses examining beta series connectivity from the MD, PUL and VL to the left LPFC are included in Supplementary Fig. 2.

3. Results

3.1. Task performance

See Table 2 for accuracy and reaction time values. The ANOVA for accuracy indicated a significant main effect of condition ($F(1,37) = 32.80$, $p < 0.001$), with both groups showing lower accuracy during the Dual condition, but no significant effect of group ($F(1,37) = 0.35$, $p = 0.56$) or group $\times$ condition interaction ($F(1,37) = 0.18$, $p = 0.68$). The ANOVA for reaction time (RT) indicated that both groups (Single =

1203 ± 169 ms, Dual = 1461 ± 242 ms) had slower RTs for the Dual compared to the Single condition ($F(1,37) = 195.68$, $p < 0.001$), and the schizophrenia group showed a trend toward slower RTs compared to the healthy group ($F(1,37) = 3.38$, $p = 0.07$). No significant group $\times$ condition interaction ($F(1,37) = 1.71$, $p = 0.20$) was found (Fig. 1B).

3.2. Cognitive demand related activation differences across the whole brain and PFC

As shown in Fig. 2A, healthy individuals showed significant differences for the Dual > Single contrast in the pre-SMA, SMA, anterior cingulate, bilateral FEF, premotor cortex, LPFC, inferior frontal gyrus, insula, sensorimotor cortex, superior and inferior parietal lobule, visual cortex, retrosplenial cortex, superior temporal gyrus, thalamus, putamen, cerebellum, right dorsolateral prefrontal cortex and left intraparietal sulcus ($p < 0.05$, FDR). The schizophrenia group showed significant differences in similar regions, including the pre-SMA/SMA, mid-cingulate, bilateral LPFC, FEF, premotor cortex, sensorimotor cortex, insula, superior temporal gyrus, thalamus, visual cortex, cerebellum, the left superior and inferior parietal lobules, intraparietal sulcus, pallidum, putamen, retrosplenial cortex and the right inferior frontal gyrus ($p < 0.05$, FDR). No significant between group differences were observed. See Supplementary Table 1 for complete results.

ROI analyses were conducted by extracting average activation signal from the 4 PFC clusters defined from the Dual > Single contrast collapsed across all subjects. Condition differences were observed for the pre-SMA/SMA ($F(1,37) = 30.78$, $p < 0.001$), the left FEF ($F(1,37) = 33.99$, $p < 0.001$), the right LPFC ($F(1,37) = 27.07$, $p < 0.001$) and left LPFC ($F(1,37) = 16.81$, $p < 0.001$). All PFC clusters showed greater activation in the Dual compared to the Single condition (Fig. 3A, Supplementary Table 2). No region showed a significant group difference or group $\times$ condition interaction effect.

3.3. Thalamic activation differences between healthy and schizophrenia groups

Voxelwise analyses of thalamus activation found significantly greater thalamus activation in the healthy compared to the schizophrenia group in the Dual > Single contrast (see Fig. 2B; $20, -20, 6$; cluster size = 270 voxels, $p < 0.05$, FDR_{SVC}).

ROI analyses were conducted by extracting average activation signals from 3 thalamic regions defined a-priori based on the Morel histological parcellation of the thalamus defined in MNI space. Mixed ANOVA of the MD ROI showed a significant main effect of condition ($F(1,37) = 29.25$, $p < 0.001$), and group ($F(1,37) = 12.28$, $p < 0.01$) but no significant group $\times$ condition interaction ($F(1,37) = 4.58$, $p = 0.117$). The PUL ROI showed a significant main effect of condition ($F(1,37) = 9.41$, $p < 0.05$), but not group ($F(1,37) = 4.61$, $p = 0.114$) or group $\times$ condition interaction ($F(1,37) = 2.98$, $p = 0.279$). The VL ROI showed a significant effect of condition ($F(1,37) = 33.30$, $p < 0.001$), a trend toward a significant effect of group ($F(1,37) = 5.49$, $p = 0.074$), but no significant group $\times$ condition interaction ($F(1,37) = 1.30$, $p = 0.265$) (see Fig. 3B, Supplementary Table 2).

3.4. Thalamus-PFC connectivity

As we were interested in how thalamus-PFC connectivity was influenced by cognitive demand in schizophrenia, we performed a beta-series connectivity analysis using the cluster within the thalamus that showed a significant group $\times$ condition interaction as the seed region (see Fig. 4). We investigated connectivity between this thalamus seed and the 4 task-based PFC ROIs that demonstrated greater BOLD response during Dual task condition compared to Single task condition (collapsed across subjects). Connectivity between the thalamus and the left FEF, pre-SMA/SMA, right LPFC or left LPFC did not show a significant main effect of condition or group. Only connectivity between the

Table 2
Task performance.

	CON		SCZ	
	Single	Dual	Single	Dual
Accuracy	90.2 $\pm$ 10.1	78.3 $\pm$ 20.4	87.8 $\pm$ 14.0	74.0 $\pm$ 26.4
Reaction time	1062 $\pm$ 157	1374 $\pm$ 233	1203 $\pm$ 169	1461 $\pm$ 242

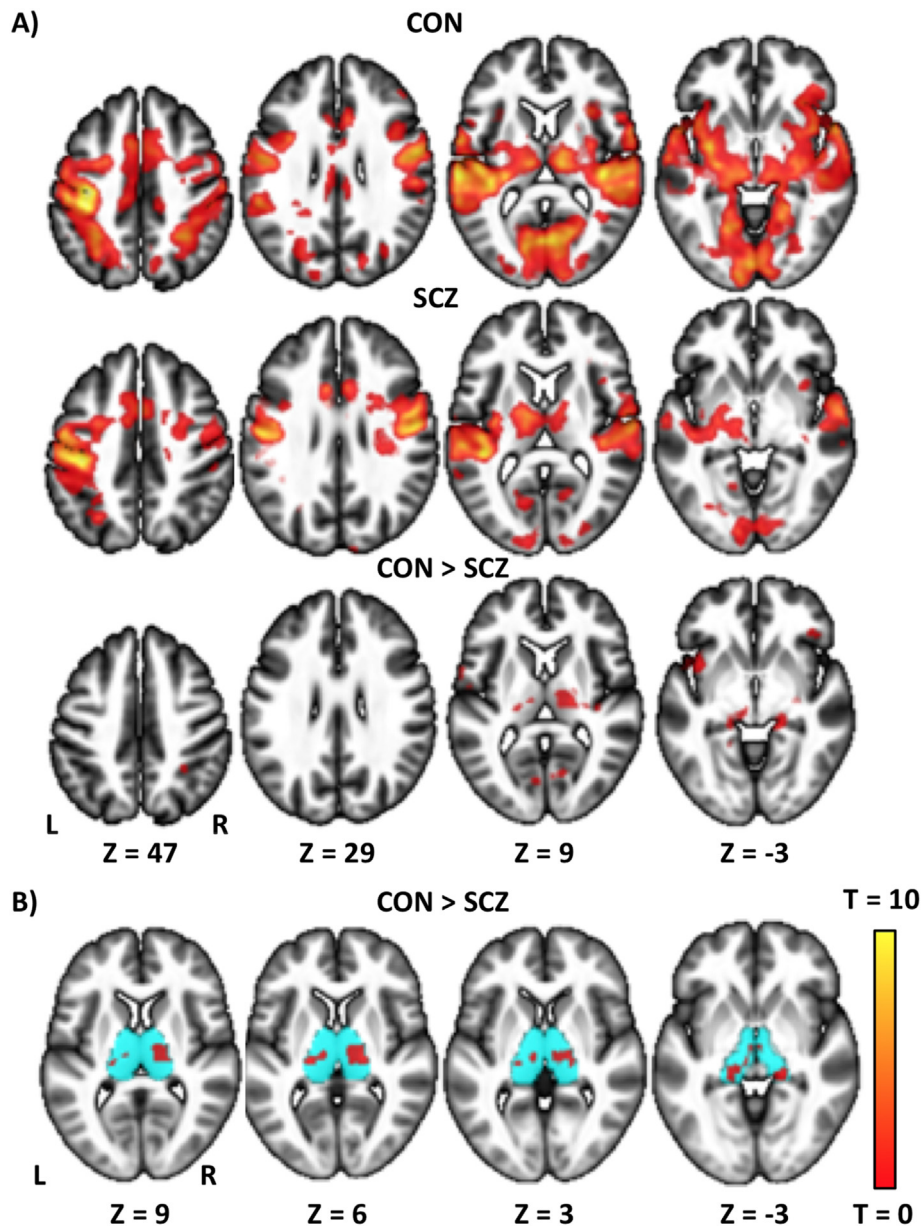


Fig. 2. A) Whole brain voxelwise analysis of brain regions showing differences in Dual > Single contrast in healthy individuals (CON), schizophrenia patients (SCZ) and CON > SCZ difference. Voxel-wise threshold of $p < 0.005$. See Supplement Table 1 for clusterwise significance. B) Dual > Single contrast masked with the Harvard-Oxford bilateral thalamus to show thalamus specific activation differences between CON and SCZ. Voxel-wise threshold $p < 0.005$, cluster significant at $FDR < 0.05_{SVC}$.

thalamus and the left LPFC showed a significant group $\times$ condition interaction ($F(1,37) = 10.23$, $p < 0.05$), such that while the healthy group showed an increase in connectivity between the Single and Dual conditions, the schizophrenia group did not show such an increase (Fig. 4, Supplementary Table 2). Beta-series connectivity results from our three Morel atlas ROIs are presented in Supplementary Fig. 2.

4. Discussion

We investigated modulation of thalamus and PFC function in schizophrenia patients using a dual task paradigm. As hypothesized, we found that in both schizophrenia and healthy individuals, thalamus and PFC activation were modulated by cognitive demand, although only the thalamus showed reduced modulation of BOLD activation in response to cognitive demand in schizophrenia, with this difference only significant in the MD thalamus. Previous literature frequently showed concurrent dysfunction of the PFC and MD regions of the thalamus in patients performing cognitive tasks (Minzenberg et al., 2009), as well as both

showing decreased metabolism during cognition, with the MD thalamus particularly affected (Hazlett et al., 2004; Lehrer et al., 2005). Interactions between the MD thalamus and PFC have been implicated in flexible, goal directed behaviors, and the MD thalamus has been particularly implicated in schizophrenia (Aleú-Paz and Giménez-Amaya, 2008; Ouhaz et al., 2018; Parnaudeau et al., 2018), showing greater volume reduction than other thalamic nuclei (Pergola et al., 2017).

Dual task paradigms in neurotypical individuals evoke a network of brain regions including the PFC and posterior parietal cortex that overlap with those observed in working memory tasks (Tamber-Rosenau et al., 2013; Tombu et al., 2011), commonly referred to as the task positive network. Disruption of PFC regions have been the focus of investigation in schizophrenia, with some studies showing increased activation, decreased activation, or no difference between groups, as in our study (Manoach, 2003). There has been less focus on changes in other regions within this network in schizophrenia, though a recent study found decreased modulation of activity in the posterior parietal cortex with increased cognitive demand in schizophrenia (Hahn et al.,

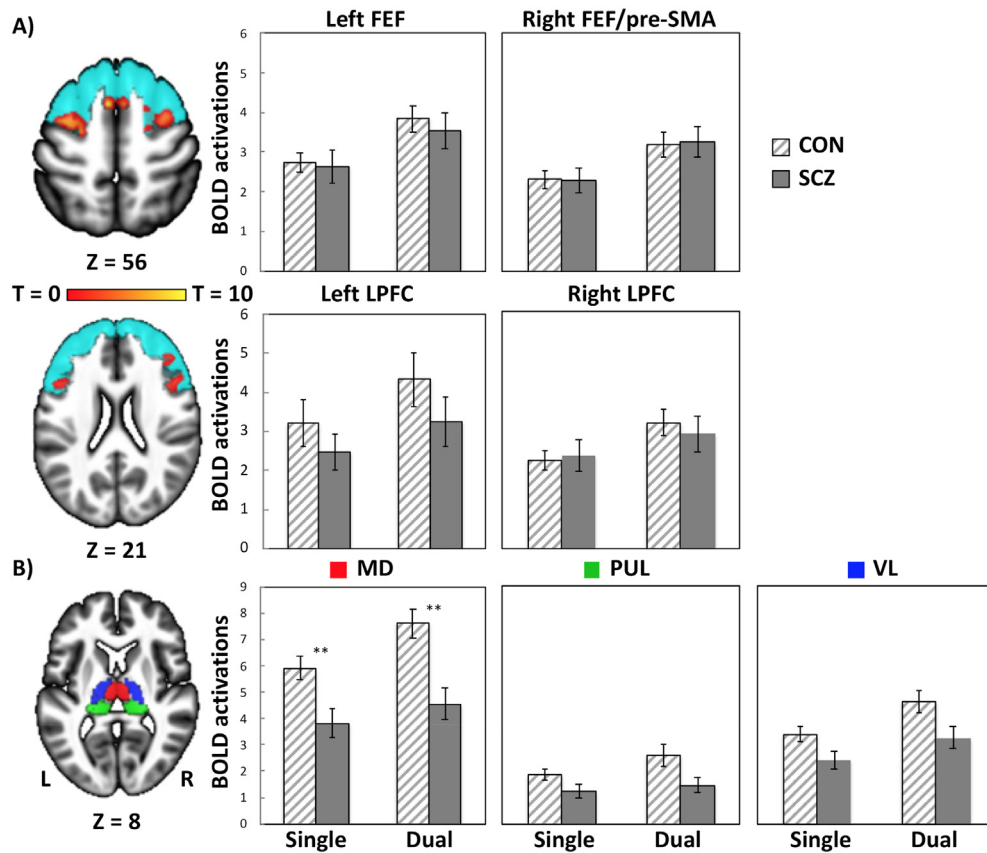


Fig. 3. Activation patterns in (A) prefrontal cortex (PFC) and (B) thalamus regions of interest (ROIs). All ROIs showed significant condition effects ($p < 0.001$), only the MD showed significant group differences ($F(1,37) = 12.28, p < 0.01$). Abbreviations: FEF = frontal eye fields; pre-SMA = pre-supplementary motor area; LPFC = lateral prefrontal cortex; MD = mediodorsal thalamus; PUL = pulvinar; VL = ventrolateral thalamus.

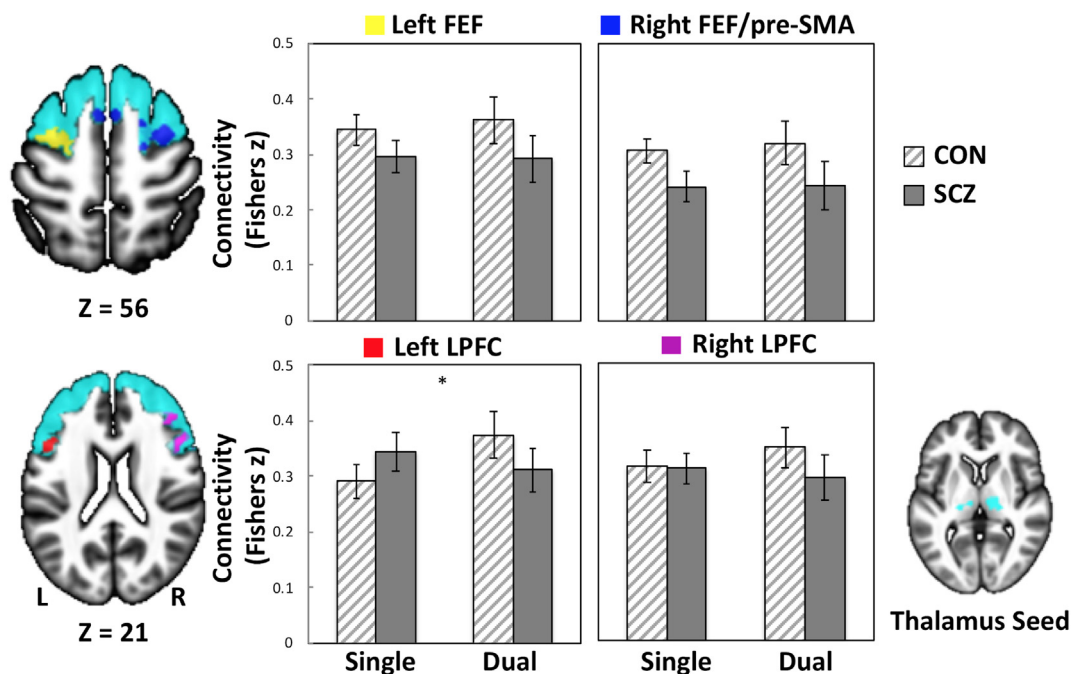


Fig. 4. Connectivity between thalamic regions (i.e. seed) that demonstrated reduced task-based activation in schizophrenia compared to healthy controls and prefrontal cortex regions of interest. The LPFC showed a significant interaction effect ($F(1,37) = 10.23, p < 0.05$, Bonferroni corrected for 4 tests), indicating our schizophrenia group did not show the cognitive demand related modulation of functional connectivity observed in our healthy group. No other main effects or interaction were significant. Abbreviations: FEF = frontal eye fields; pre-SMA = pre-supplementary motor area; LPFC = lateral prefrontal cortex.

2018). We found that an area within the thalamus covering the mediodorsal, lateral and posterior thalamus also showed reduced modulation by cognitive demand in schizophrenia, suggesting that regions within the task positive network other than the PFC are also disrupted in schizophrenia.

In addition to thalamus activation, thalamus-PFC connectivity with the LPFC also showed reduced modulation by task demand in schizophrenia. Compared to the right hemisphere, the left thalamus and the left PFC has shown reduced structural connectivity in schizophrenia (Giraldo-Chica et al., 2018). This region of the PFC has previously been identified as an a-modal central bottleneck, important for resolving dual task competition (Dux et al., 2006, 2009). In studies of working memory load, only the left LPFC showed an interaction between working memory load and group such that patients showed lower activation increases with working memory load (Cannon et al., 2005; Perlstein et al., 2003), as well as an interaction between working memory load and performance such that poorer performing patients showed decreased activation and higher performing patients showed increased activation compared to healthy individuals, with this effect most prominent in the left hemisphere (Karlsgodt et al., 2009). No other PFC region tested showed a reduction in task-based modulation, suggesting that thalamocortical connectivity between the thalamus and the left LPFC may be particularly impaired in patients.

Studies of thalamocortical connectivity at rest consistently find reduced connectivity between the thalamus and prefrontal cortex (Anticevic et al., 2013, 2014; Klingner et al., 2014; Lui et al., 2015; Welsh et al., 2010; Woodward and Heckers, 2016; Woodward et al., 2012). Decreased thalamus-PFC resting state connectivity has been positively associated with cognition; although the association was relatively weak (Woodward and Heckers, 2016). Further, thalamus-PFC connectivity increased after cognitive remediation training, but not computer skills training, with this increase positively associated with increases in cognitive scores (MATRICS scores) (Ramsay et al., 2017), implicating resting state thalamocortical connectivity in cognitive function in schizophrenia.

In contrast to resting state, few studies have investigated thalamocortical connectivity during cognitive tasks. Such studies typically find increased connectivity in patients during task. In a structural equation model including the dorsolateral and ventrolateral PFC, parietal cortex, thalamus and cerebellum during a working memory task, patients showed increased path coefficients between the thalamus and ventrolateral PFC in task compared to baseline (Schlösser et al., 2003). In another study, patients showed lower connectivity from the right dorsolateral PFC to right thalamus, and greater connectivity from the dorsal anterior cingulate to thalamus during a cognitive control task (Wagner et al., 2013). In addition, there was a significant positive correlation between right dorsolateral PFC-thalamus endogenous connectivity and fractional anisotropy (a measure of white matter integrity) in the white matter tract between the frontal cortex and thalamus (Wagner et al., 2015), suggesting that changes in PFC-thalamus connectivity have an underlying structural basis. In a single pulse transcranial magnetic stimulation (TMS) study, thalamic response after stimulation was significantly lower in patients compared to healthy controls, with the magnitude of the TMS-evoked response predicted by coupling between the thalamus and PFC (Guller et al., 2012), providing evidence of a direct association between evoked brain responses in the cortex and thalamic function and connectivity. Our study adds to the literature by suggesting that thalamus-PFC connectivity during task is not a static increase, rather that the relationship may depend on cognitive demand.

Our investigation had several limitations. The current task only included two levels of difficulty, which precluded us from investigating non-linear changes in activation and connectivity. Our design did not allow us to test if activation within the thalamus also demonstrates an inverted-U shaped activation pattern similar to the PFC. Another limitation of our design was our comparison of Dual compared to Single conditions. Although our task was designed to investigate thalamic

responses to cognitive demand, it is possible that different cognitive mechanisms may be required for Single and Dual conditions, therefore we cannot rule out the possibility that our results reflect differences in cognitive processes underlying the two conditions rather than cognitive demand. Additionally, most of our patients were on antipsychotic medication, therefore interpretation of our results must take into account medication effects. Finally, statistical power to detect group effects was limited by the modest sample sizes. Several results, including task performance and differences in activation, reached trend significance suggesting that additional effects may have been detected if sample sizes were larger.

In conclusion, patients are less able to appropriately modulate their thalamus activation and thalamus connectivity with the left LPFC based on task requirements.

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CRediT authorship contribution statement

Anna S. Huang: Conceptualization, Data curation, Formal analysis, Writing - original draft, Writing - review & editing. **Baxter P. Rogers:** Methodology, Software, Validation, Data curation, Investigation, Writing - review & editing. **Neil D. Woodward:** Funding acquisition, Conceptualization, Resources, Supervision, Writing - review & editing.

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Appendix A. Supplementary data

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References

- Alelú-Paz, R., Giménez-Amaya, J.M., 2008. The mediodorsal thalamic nucleus and schizophrenia. *J. Psychiatry Neurosci.* 33 (6), 489–498.
- Andreasen, N.C., 1997. The role of the thalamus in schizophrenia. *Can. J. Psychiatr.* 42 (1), 27–33.
- Andrews, J., Wang, L., Csernansky, J.G., Gado, M.H., Barch, D.M., 2006. Abnormalities of thalamic activation and cognition in schizophrenia. *Am. J. Psychiatry* 163 (3), 463–469.
- Anticevic, A., Cole, M.W., Repovs, G., Murray, J.D., Brumbaugh, M.S., Winkler, A.M., ... Glahn, D.C., 2013. Characterizing thalamo-cortical disturbances in schizophrenia and bipolar illness. *Cereb. Cortex* 24 (12), 3116–3130.
- Anticevic, A., Yang, G., Savic, A., Murray, J.D., Cole, M.W., Repovs, G., ... Glahn, D.C., 2014. Mediodorsal and visual thalamic connectivity differ in schizophrenia and bipolar disorder with and without psychosis history. *Schizophr. Bull.* 40 (6), 1227–1243.
- Birn, R.M., Cox, R.W., Bandettini, P.A., 2004. Experimental designs and processing strategies for fMRI studies involving overt verbal responses. *NeuroImage* 23 (3), 1046–1058.
- Bor, J., Brunelin, J., Sappey-Mariniér, D., Ibarrola, D., d'Amato, T., Suaud-Chagny, M.-F., Saoud, M., 2011. Thalamus abnormalities during working memory in schizophrenia. *An fMRI study. Schizophr. Res.* 125 (1), 49–53.
- Bridge, H., Leopold, D.A., Bourne, J.A., 2016. Adaptive pulvinar circuitry supports visual cognition. *Trends Cogn. Sci.* 20 (2), 146–157.
- Callicott, J.H., Bertolino, A., Mattay, V.S., Langheim, F.J., Duyn, J., Coppola, R., ... Weinberger, D.R., 2000. Physiological dysfunction of the dorsolateral prefrontal cortex in schizophrenia revisited. *Cereb. Cortex* 10 (11), 1078–1092.
- Camchong, J., Dyckman, K.A., Chapman, C.E., Yamasak, N.E., McDowell, J.E., 2006. Basal ganglia-thalamocortical circuitry disruptions in schizophrenia during delayed response tasks. *Biol. Psychiatry* 60 (3), 235–241.
- Cannon, T.D., Glahn, D.C., Kim, J., Van Erp, T.G.M., Karlsgodt, K., Cohen, M.S., ... Shirinyan, D., 2005. Dorsolateral prefrontal cortex activity during maintenance and manipulation of information in working memory in patients with schizophrenia. *Arch. Gen. Psychiatry* 62 (10), 1071–1080.
- Choi, J.-S., Park, J.-Y., Jung, M.H., Jang, J.H., Kang, D.-H., Jung, W.H., ... Kwon, J.S., 2012. Phase-specific brain change of spatial working memory processing in genetic and ultra-high risk groups of schizophrenia. *Schizophr. Bull.* 38 (6), 1189–1199.

- Cisler, J.M., Bush, K., Steele, J.S., 2014. A comparison of statistical methods for detecting context-modulated functional connectivity in fMRI. *NeuroImage* 84, 1042–1052.
- Desikan, R.S., Ségonne, F., Fischl, B., Quinn, B.T., Dickerson, B.C., Blacker, D., ... Killiany, R.J., 2006. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *NeuroImage* 31 (3), 968–980.
- Dux, P.E., Ivanoff, J., Asplund, C.L., Marois, R., 2006. Isolation of a central bottleneck of information processing with time-resolved fMRI. *Neuron* 52 (6), 1109–1120.
- Dux, P.E., Tombu, M.N., Harrison, S., Rogers, B.P., Tong, F., Marois, R., 2009. Training improves multitasking performance by increasing the speed of information processing in human prefrontal cortex. *Neuron* 63 (1), 127–138.
- First, M.B., Gibbon, M., Spitzer, R.L., Williams, J.B.W., 1996. User's Guide for the Structured Clinical Interview for DSM-IV Axis I Disorders—Research Version. Biometrics Research Department, New York State Psychiatric Institute, New York.
- Giraldo-Chica, M., Woodward, N.D., 2017. Review of thalamocortical resting-state fMRI studies in schizophrenia. *Schizophr. Res.* 180, 58–63.
- Giraldo-Chica, M., Rogers, B.P., Damon, S.M., Landman, B.A., Woodward, N.D., 2018. Prefrontal-thalamic anatomical connectivity and executive cognitive function in schizophrenia. *Biol. Psychiatry* 83 (6), 509–517.
- Guller, Y., Ferrarelli, F., Shackman, A.J., Sarasso, S., Peterson, M.J., Langheim, F.J., ... Postle, B.R., 2012. Probing thalamic integrity in schizophrenia using concurrent transcranial magnetic stimulation and functional magnetic resonance imaging. *Arch. Gen. Psychiatry* 69 (7), 662–671.
- Gur, R.E., Turetsky, B.I., Loughead, J., Snyder, W., Kohler, C., Elliott, M., ... Gur, R.C., 2007. Visual attention circuitry in schizophrenia investigated with oddball event-related functional magnetic resonance imaging. *Am. J. Psychiatry* 164 (3), 442–449.
- Haber, S.N., Calzavara, R., 2009. The cortico-basal ganglia integrative network: the role of the thalamus. *Brain Res. Bull.* 78 (2–3), 69–74.
- Haber, S.N., McFarland, N.R., 2001. The place of the thalamus in frontal cortical-basal ganglia circuits. *Neuroscientist* 7 (4), 315–324.
- Hahn, B., Robinson, B.M., Leonard, C.J., Luck, S.J., Gold, J.M., 2018. Posterior parietal cortex dysfunction is central to working memory storage and broad cognitive deficits in schizophrenia. *J. Neurosci.* 38 (39), 8378–8387.
- Hazlett, E.A., Buchsbaum, M.S., Kemether, E., Bloom, R., Platholi, J., Brickman, A.M., ... Byrne, W., 2004. Abnormal glucose metabolism in the mediodorsal nucleus of the thalamus in schizophrenia. *Am. J. Psychiatry* 161 (2), 305–314.
- Hazlett, E.A., Buchsbaum, M.S., Zhang, J., Newmark, R.E., Glanton, C.F., Zelmanova, Y., ... Siever, L.J., 2008. Frontal-striatal-thalamic mediodorsal nucleus dysfunction in schizophrenia-spectrum patients during sensorimotor gating. *NeuroImage* 42 (3), 1164–1177.
- Jones, E.G., 2007. *The Thalamus*. second edition. Cambridge University Press, New York.
- Karlsgodt, K.H., Sanz, J., van Erp, T.G.M., Bearden, C.E., Nuechterlein, K.H., Cannon, T.D., 2009. Re-evaluating dorsolateral prefrontal cortex activation during working memory in schizophrenia. *Schizophr. Res.* 108 (1–3), 143–150.
- Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr. Bull.* 13 (2), 261–276.
- Kiehl, K.A., Liddle, P.F., 2001. An event-related functional magnetic resonance imaging study of an auditory oddball task in schizophrenia. *Schizophr. Res.* 48 (2–3), 159–171.
- Klingner, C.M., Langbein, K., Dietzek, M., Smesny, S., Witte, O.W., Sauer, H., Nenadic, I., 2014. Thalamocortical connectivity during resting state in schizophrenia. *Eur. Arch. Psychiatry Clin. Neurosci.* 264 (2), 111–119.
- Kumari, V., Antonova, E., Geyer, M.A., Flytche, D., Williams, S.C.R., Sharma, T., 2007. A fMRI investigation of startle gating deficits in schizophrenia patients treated with typical or atypical antipsychotics. *Int. J. Neuropsychopharmacol.* 10 (4), 463–477.
- Laurens, K.R., Kiehl, K.A., Ngan, E.T.C., Liddle, P.F., 2005. Attention orienting dysfunction during salient novel stimulus processing in schizophrenia. *Schizophr. Res.* 75 (2–3), 159–171.
- Lehrer, D.S., Christian, B.T., Mantil, J., Murray, A.C., Buchsbaum, B.R., Oakes, T.R., ... Buchsbaum, M.S., 2005. Thalamic and prefrontal FDG uptake in never medicated patients with schizophrenia. *Am. J. Psychiatry* 162 (5), 931–938.
- Lui, S., Yao, L., Xiao, Y., Keedy, S.K., Reilly, J.L., Keefe, R.S., ... Sweeney, J.A., 2015. Resting-state brain function in schizophrenia and psychotic bipolar probands and their first-degree relatives. *Psychol. Med.* 45 (1), 97–108.
- Manoach, D.S., 2003. Prefrontal cortex dysfunction during working memory performance in schizophrenia: reconciling discrepant findings. *Schizophr. Res.* 60 (2–3), 285–298.
- Minzenberg, M.J., Laird, A.R., Thelen, S., Carter, C.S., Glahn, D.C., 2009. Meta-analysis of 41 functional neuroimaging studies of executive function in schizophrenia. *Arch. Gen. Psychiatry* 66 (8), 811–822.
- Mitchell, A.S., 2015. The mediodorsal thalamus as a higher order thalamic relay nucleus important for learning and decision-making. *Neurosci. Biobehav. Rev.* 54, 76–88.
- Morel, A., Magnin, M., Jeanmonod, D., 1997. Multiarchitectonic and stereotactic atlas of the human thalamus. *J. Comp. Neurol.* 387 (4), 588–630.
- Niemann, K., Mennicken, V.R., Jeanmonod, D., Morel, A., 2000. The Morel stereotactic atlas of the human thalamus: atlas-to-MR registration of internally consistent canonical model. *NeuroImage* 12 (6), 601–616.
- Ouhaz, Z., Fleming, H., Mitchell, A.S., 2018. Cognitive functions and neurodevelopmental disorders involving the prefrontal cortex and mediodorsal thalamus. *Front. Neurosci.* 12, 33.
- Parnadeau, S., Bolkan, S.S., Kellendonk, C., 2018. The mediodorsal thalamus: an essential partner of the prefrontal cortex for cognition. *Biol. Psychiatry* 83 (8), 648–656.
- Pergola, G., Trizio, S., Di Carlo, P., Taurisano, P., Mancini, M., Amoroso, N., ... Blasi, G., 2017. Grey matter volume patterns in thalamic nuclei are associated with familial risk for schizophrenia. *Schizophr. Res.* 180, 13–20.
- Perlstein, W.M., Dixit, N.K., Carter, C.S., Noll, D.C., Cohen, J.D., 2003. Prefrontal cortex dysfunction mediates deficits in working memory and prepotent responding in schizophrenia. *Biol. Psychiatry* 53 (1), 25–38.
- Ragland, J.D., Gur, R.C., Valdez, J.N., Loughhead, J., Elliott, M., Kohler, C., ... Gur, R.E., 2005. Levels-of-processing effect on frontotemporal function in schizophrenia during word encoding and recognition. *Am. J. Psychiatry* 162 (10), 1840–1848.
- Ramsay, I.S., Nienow, T.M., MacDonald 3rd, A.W., 2017. Increases in intrinsic thalamocortical connectivity and overall cognition following cognitive remediation in chronic schizophrenia. *Biol. Psychiatry Cogn. Neurosci. Neuroimaging* 2 (4), 355–362.
- Rissman, J., Gazzaley, A., D'Esposito, M., 2004. Measuring functional connectivity during distinct stages of a cognitive task. *NeuroImage* 23 (2), 752–763.
- Salgado-Pineda, P., Junqué, C., Vendrell, P., Baeza, I., Bargalló, N., Falcón, C., Bernardo, M., 2004. Decreased cerebral activation during CPT performance: structural and functional deficits in schizophrenic patients. *NeuroImage* 21 (3), 840–847.
- Schlösser, R.G.M., Gesierich, C.A.T., Kaufmann, B., Vucurevic, G., Stoeter, P., 2003. Altered effective connectivity in drug free schizophrenic patients. *NeuroReport* 14 (17), 0959–4965.
- Schlösser, R.G.M., Koch, K., Wagner, G., Nenadic, I., Roebel, M., Schachtzabel, C., ... Sauer, H., 2008. Inefficient executive cognitive control in schizophrenia is preceded by altered functional activation during information encoding: an fMRI study. *Neuropsychologia* 46 (1), 336–347.
- Schneider, F., Habel, U., Reske, M., Kellermann, T., Stöcker, T., Shah, N.J., ... Gaebel, W., 2007. Neural correlates of working memory dysfunction in first-episode schizophrenia patients: an fMRI multi-center study. *Schizophr. Res.* 89 (1–3), 198–210.
- Skåtun, K.C., Kaufmann, T., Brandt, C.L., Doan, N.T., Alnæs, D., Tønnesen, S., ... Westlye, L.T., 2017. Thalamo-cortical functional connectivity in schizophrenia and bipolar disorder. *Brain Imaging and Behav.* <https://doi.org/10.1007/s11682-017-9714-y>.
- Tamber-Rosenau, B.J., Dux, P.E., Tombu, M.N., Asplund, C.L., Marois, R., 2013. Amodal processing in human prefrontal cortex. *J. Neurosci.* 33 (28), 11573–11587.
- Tombu, M.N., Asplund, C.L., Dux, P.E., Godwin, D., Martin, J.W., Marois, R., 2011. A Unified attentional bottleneck in the human brain. *Proc. Natl. Acad. Sci. U. S. A.* 108 (33), 13426–13431.
- Tregellas, J.R., Davalos, D.B., Rojas, D.C., Waldo, M.C., Gibson, L., Wylie, K., ... Freedman, R., 2007. Increased hemodynamic response in the hippocampus, thalamus and prefrontal cortex during abnormal sensory gating in schizophrenia. *Schizophr. Res.* 92 (1–3), 262–272.
- Tregellas, J.R., Ellis, J., Shatti, S., Du, Y.P., Rojas, D.C., 2009. Increased hippocampal, thalamic, and prefrontal hemodynamic response to an urban noise stimulus in schizophrenia. *Am. J. Psychiatry* 166 (3), 354–360.
- van Erp, T.G.M., Hibar, D.P., Rasmussen, J.M., Glahn, D.C., Pearlson, G.D., Andreassen, O.A., ... Turner, J.A., 2016. Subcortical brain volume abnormalities in 2028 individuals with schizophrenia and 2540 healthy controls via the ENIGMA consortium. *Mol. Psychiatry* 21 (4), 547–553.
- Wagner, G., Koch, K., Schachtzabel, C., Schultz, C.C., Gaser, C., Reichenbach, J.R., ... Schlösser, R.G., 2013. Structural basis of the fronto-thalamic dysconnectivity in schizophrenia: a combined DCM-VBM study. *Neuroimage Clin.* 3, 95–105.
- Wagner, G., De la Cruz, F., Schachtzabel, C., Güllmar, D., Schultz, C.C., Schlösser, R.G., ... Koch, K., 2015. Structural and functional dysconnectivity of the fronto-thalamic system in schizophrenia: a DCM-DTI study. *Cortex* 66, 35–45.
- Wang, H.-L.S., Rau, C.-L., Li, Y.-M., Chen, Y.-P., Yu, R., 2015. Disrupted thalamic resting-state functional networks in schizophrenia. *Front. Behav. Neurosci.* 9, 45.
- Wechsler, D., 2001. *Wechsler Test of Adult Reading: WTAR*. Psychological Corporation.
- Welsh, R.C., Chen, A.C., Taylor, S.F., 2010. Low-frequency BOLD fluctuations demonstrate altered thalamocortical connectivity in schizophrenia. *Schizophr. Bull.* 36 (4), 713–722.
- Woodward, N.D., Heckers, S., 2016. Mapping thalamocortical functional connectivity in chronic and early stages of psychotic disorders. *Biol. Psychiatry* 79 (12), 1016–1025.
- Woodward, N.D., Karbasforoushan, H., Heckers, S., 2012. Thalamocortical dysconnectivity in schizophrenia. *Am. J. Psychiatry* 169 (10), 1092–1099.