THESIS

LARGE SCALE BRAIN NETWORK MENTAL WORKLOAD ENGAGEMENT IN SCHIZOPHRENIA

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ABSTRACT

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Objective: Cognitive deficits in patients diagnosed with schizophrenia are a core feature of the disorder. There are currently no treatments for these cognitive deficits. Our aim is to examine and compare patterns of increased versus decreased activity in the central executive network (CEN), salience network (SN), and default mode network (DMN) between healthy controls (HC) and patients diagnosed with schizophrenia (SZ) as well as to explore the influence of task load on these networks between HC and SZ.

Method: Analyses focused on a secondary dataset comprising Blood Oxygen-Level Dependent (BOLD) data collected from 25 HC and 27 SZ who completed a working memory (WM) task (N-back) with 5 load conditions while undergoing functional magnetic resonance imaging (fMRI). Region of interest (ROI) data were analyzed using linear mixed-effects models. Dynamic causal modeling (DCM) was used in an exploratory analysis to examine working memory load input to these networks.

Results: Group activation differences were found in the posterior salience network (pSN), default mode network (DMN), dorsal default mode network (dDMN), and ventral default mode network (vDMN) showing greater activity for SZ. Specifically, pSN, SMN, dDMN, and vDMN all showed increased activity in SZ compared to HC. The curve of brain activity was consistent between HC and SZ with the exception of the

vDMN, where HC show greater activation at modest mental workload (quadratic curve) and SZ showed greater brain activation at lower mental workload (linear). In the CEN, there were no group differences, and the response curve was the same for both groups. In DCM analysis, working memory load acted as an input on different networks between HC and SZ.

Conclusions: These group differences demonstrate network difference between HC and SZ and could show value in treatments targeting cognitive deficits in SZ from a large-scale brain network connectivity perspective. Future studies are needed to confirm these results with higher sample size in order to examine potential subtleties of interactions between these networks.

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INTRODUCTION

Schizophrenia is a debilitating mental illness that affects between 0.5 and 1% of the world's population (Knapp et al., 2004). This disorder also increases early mortality rate by two to three times (Laursen et al., 2014). Symptoms typically manifest in what is considered the 'prime of life', between the ages of 18 and 25, and then persist throughout adulthood (de Girolamo et al., 2019). There is a desperate need to better understand, treat, and minimize the impact of this disorder.

Schizophrenia diagnosis requires the presence of positive and/or negative symptoms (American Psychiatric Association, 2013). Positive symptoms include: (1) delusions, or fixed beliefs that do not change when presented with conflicting evidence; (2) hallucinations, or sensory perception-like experiences that occur separate from outside stimuli; and (3) disorganized thinking, speech, and or motor behavior, which is characterized by switching from one subject to another and or non-goal-oriented motor behavior. Negative symptoms are generally characterized by experiential (i.e., avolition and anhedonia) or expressive (i.e., affective blunting/flattening and alogia) features. Although not required for diagnosis, cognitive deficits are a third common feature of schizophrenia.

Cognitive deficits, which have been associated with psychosis since the writing of Kraepelin (Kahn, 2014), are not an incidental feature of the disorder. Rather, cognitive deficits more strongly predict functional outcomes than do positive and negative symptoms (Bowie & Harvey, 2006; Carter & Barch, 2007; Green et al., 2000). Despite

this, the search for effective procognitive therapeutics remains elusive. A possible explanation is that little is known about the brain network basis of these deficits. The goal of this thesis is to characterize brain network disruption in schizophrenia, and by doing so shed light on possible causes of global cognitive disfunction in the disorder.

Cognitive Deficits in Schizophrenia

Cognitive deficits associated with schizophrenia are global. Most notably, patients show deficits in general intelligence that are typically in the moderate effect size range (Woodberry et al., 2008). Attenuated deficits are present in patients who are later diagnosed with schizophrenia even before they experience their first psychotic episode (Aylward et al., 1984; David et al., 1997; Reichenberg et al., 2006). Evidence also suggests that people who develop schizophrenia have premorbid IQs that are lower than that of their siblings (Lane & Albee, 1965).

Patients diagnosed with schizophrenia have deficits across nearly all cognitive domains including general intelligence, attention, motivation, verbal ability, and working memory (Aylward et al., 1984; David et al., 1997; Kubicki et al., 2009; Lane & Albee, 1965; Nuechterlein & Dawson, 1984; Oker et al., 2019; Woodberry et al., 2008). Of these domains, working memory (WM) is among the most prominent and well-studied (Barch & Smith, 2008; Kalkstein et al., 2010; Lee & Park, 2005), and most strongly connected to many functional outcomes (Green et al., 2000). WM has been defined as " … mechanisms or processes that are involved in the control, regulation and active maintenance of task-relevant information in the service of complex cognition … " (Miyake & Shah, 1999). WM is also strongly related to effort and motivation in that high levels of working memory load exert a heavier toll on mental workload (the total amount

of a person's mental resources that are invested in a task). Notably, SZ also have deficits in effort (Barch & Dowd, 2010; Culbreth et al., 2016). Indeed, it has been suggested that some aspects of patients' cognitive deficits on WM and other demanding cognitive tasks can be explained by a failure to engage mental workload (Oker et al., 2019). These issues make treating cognitive deficits in SZ challenging as the cognitive basis for these deficits are ambiguous.

Treatment of Schizophrenia

Treatment for schizophrenia relies heavily on pharmacological interventions, though psychosocial interventions are also recommended (Kane & Marder, 1993; Keepers et al., 2020). Antipsychotic treatments typically target specific dopamine and serotonin and norepinephrine pathways (Kane & Marder, 1993; Stępnicki et al., 2018). These medications are, in general, effective in reducing the severity of hallucinations and delusions (Stępnicki et al., 2018). However, they have less of an impact on negative symptoms (Leucht et al., 2009), and have no positive effect on cognitive functioning. Antipsychotics can be associated with iatrogenic effects for cognition. Specifically, many antipsychotics have anticholinergic properties, and these anticholinergic effects have been associated with dose-dependent deficits in cognitive functioning (Joshi et al., 2021). Not only do common pharmacologic treatments for schizophrenia not improve cognition, but they can also exacerbate preexisting cognitive deficits. Moreover, there are no drugs that are approved for the treatment of cognitive deficits (Stępnicki et al., 2018).

Brain Differences in Schizophrenia

A possible explanation for why cognitive treatments for schizophrenia have proven elusive is that we lack a comprehensive understanding of the brain-basis of cognitive psychopathology (Carter & Barch, 2007). Gaining a better understanding of cognitive and brain abnormalities in schizophrenia could lead to more targeted treatments (Carter & Barch, 2007). What is known is that patients show widespread differences in the brain relative to healthy controls (HC), and that these differences are associated with cognitive deficits (Barch, 2005). Brain abnormalities associated with psychosis are both structural and functional (Chua & McKenna, 1995). The affected regions are found throughout the brain, but especially in frontal and parietal cortices, as well as the striatum (Zhao et al., 2018).

A truism of schizophrenia is that there is no one brain location that explains deficits. As noted by Swerdlow (1991), "The 'hole' thing is wrong." However, it is important to note that several key brain areas that show abnormal structure and function in schizophrenia are considered to be functional nodes within interrelated brain networks. These include the dorsolateral prefrontal cortex, posterior parietal cortex, medial prefrontal cortex, angular gyrus, insula, and anterior cingulate cortex (Manoliu et al., 2014; Menon, 2011). Understanding how these brain regions function, or misfunction, in the context of network difference in patients with schizophrenia (SZ) is an increasingly important area of research.

Brain Network Differences

Patients diagnosed with schizophrenia show disruption in several brain networks, namely, the default mode network (DMN), the salience network (SN), and the

central executive network (CEN). This is important because the interplay of these three networks is critical to successful cognitive task performance (Menon, 2011).

The CEN (also referred to as the frontoparietal network) is a brain network that shows increased activity during task engagement (van den Heuvel & Hulshoff Pol, 2010). The network's major nodes include the dorsolateral prefrontal cortex (dlPFC) and the posterior parietal cortex (PPC). These cortical areas are observed to be functionally connected when an individual is 'on task'; that is, purposefully engaged with a cognitive task (Cao et al., 2016). More granularly, the dlPFC is known to be more active during tasks that involve decision making and WM (Philiastides et al., 2011; Schon et al., 2013), and the PPC known to be more active during a variety of cognitive tasks, but especially tasks that involve spatial reasoning, visual WM, and calculation (Berryhill & Olson, 2008; Malhotra et al., 2009).

The DMN is known to show increased activity during breaks, rest, and self-referential activities such as daydreaming (van den Heuvel & Hulshoff Pol, 2010). The network's major nodes include the medial prefrontal cortex (mPFC), the posterior cingulate cortex (PCC), and the angular gyrus (AG). The mPFC is known to be more active during self-referential decision making and reward learning (Euston et al., 2012), the PCC is known to be more active during self-referential memory and emotional salience (Leech & Sharp, 2014), and the AG is known to be more active during with language, spatial cognition, and attention (Cattaneo et al., 2009).

The SN is known to show increased activity when tasks require particular stimuli to stand out from others (van den Heuvel & Hulshoff Pol, 2010). The network's major nodes include the anterior insula (aINS) and the anterior cingulate cortex (ACC).

The aINS is known to be more active during tasks that require multi-modal sensory (audio-visual) sensory processing, body awareness, interoception, and emotional salience (Stephani et al., 2011). The ACC is known to be more active during tasks that require error detection and monitoring, reward learning, and emotional modulation (Vogt, 2005).

In the 'triple network model', healthy or neurotypical individuals show an inverse pattern of activation in the DMN and CEN with the SN mediating between the two (Li et al., 2018; Menon, 2011). That is, when an individual is engaged in a task, the CEN is more active and the DMN is less active and vice-versa when the individual is not engaged in a task. The SN appears to play an important role in the relationship between the two (Li et al., 2018; Menon, 2011).

While the DMN, CEN, and SN appear to show naturally balanced patterns of activity in healthy or neurotypical individuals, they appear to be disrupted in many psychiatric and neurological disorders (Menon, 2011). This is particularly true of schizophrenia (Calhoun, 2009). Patients diagnosed with schizophrenia exhibit functional abnormalities between the CEN, DMN, and SN and the balance of the triple network model seems to be abnormal (Jeong & Kubicki, 2010). In particular, there is evidence of less suppression of the DMN during task activity and also less engagement of the CEN (Zhou et al., 2016). Notably, network activity is not just related to cognitive deficits, but also symptoms and functional outcomes in a positive or negative direction depending on the network (Cao et al., 2016; Hare et al., 2019), suggesting that elucidating these abnormalities could lead to better target treatment and improved

functional outcomes. Indeed, network abnormalities have been linked to improvements in treatment (Lin et al., 2021).

Aims

Decades of research have now clearly established that patients with SZ show impairments in cognitive ability and effort, and that the functional activity of several important brain networks is disrupted in schizophrenia. However, we do not know how these networks engage and disengage interactively under mental workload. It is possible that SZ results in the disruption of normal connectivity within the triple network model under workload, thereby explaining, in part, why patients show both poor cognitive ability and poor functioning. Understanding the nature of this abnormality activity could prove crucial to developing effective cognitive treatments for patients. The first aim is to examine and compare patterns of increased versus decreased activity in the CEN, DMN, and SN between HC and SZ. In particular, I will examine how changing mental workload modulates brain network engagement. Hypothesis 1 is that patients diagnosed with schizophrenia will show less mental workload-based modulation of these networks. The second, exploratory aim is to examine how N-back level (task-load) acts as an input on these large-scale brain networks to see if there are differences between HC and SZ. Specifically, I wanted to know whether external demands of cognitive task difficulty might differentially affect these three networks between HC and SZ.

METHOD

Participants

Data were selected from a previously competed study (Thomas et al., 2021). Specifically, 27 patients diagnosed with schizophrenia or schizoaffective disorder and 25 healthy controls were recruited to participate in a brain imaging study of cognitive deficits in psychosis. The inclusion criteria were unimpaired hearing and eyesight and English fluency and between 18 and 70 years of age. Exclusion criteria were inability to give consent, positive drug toxicology screen, substance dependency in the last 6 months, pregnancy, contraindications for MRI, significant past head injury, significant extrapyramidal symptoms or tardive dyskinesia, and significant other medical or neurological diagnoses. Controls were additionally excluded if they were enrolled in special education courses during school or met diagnostic criteria for any psychosis spectrum disorder or bipolar disorder. Left-handedness was not excluded, as this trait tends to be higher in patients diagnosed with schizophrenia (although the proportion in this study was nearly identical to HCs). Clinical diagnoses were verified by a licensed clinical psychologist using structured interviews (Thomas et al., 2021).

Design

The original experimental design was a two-by-five mixed factorial. The between-subjects factor was population (i.e., HC vs. SZ; 2 levels). The within-subjects factor was WM load (5 levels). To manipulate load, participants were administered the N-back task. The N-back task is a measure of WM that requires examinees to monitor a continuous stream of stimuli (pseudowords) and respond each time an item is repeated from N before. Three N-back runs were created, each consisting of 5 blocks of trials (i.e.,

1- through 5-back load conditions). One run was administered outside of the scanner and the remaining two were administered within the scanner. Blocks were counterbalanced over runs. The task was administered using PsychoPy (Peirce et al., 2019). Pseudowords were presented in white font on a black background for 2500ms with a 500ms inter-item-interval. The timing was constrained so that each block would last exactly 60s. Blocks were separated by 20s intervals (with a fixation cross).

Preprocessing

Imaging data was previously processed using local scripts as well as software from Analysis of Functional NeuroImages (AFNI; Ver. 18.1.14) (Cox, 1996) and FMRIB Software Library (FSL; Ver. 5.0.10) (Jenkinson et al., 2012) to process the structural and functional images. In AFNI non-brain tissue was removed from structural images, and adjustments to registration were made to automatically warp the images into Talairach space (Talairach & Tournoux, 1988) using the ICBM-452 brain template (Rex et al., 2003). Magnetic field distortions were corrected using FSL's TOPUP tool. Scanner artifacts (spikes) were removed using AFNI's 3dDespike tool. Next, AFNI's alignment tool (align_epi_anat) was used to co-register functional images (3dvolreg) within the time-series and then align them to the (unregistered) structural images (3dAllineate). Given the block design, the data were not time shifted (Poldrack et al., 2011).

In order to account for physiological motion, respiration and cardiac activity were acquired in parallel with the functional images and converted to sines and cosines of the first and second phase cycles modeling the physiological activity (Glover et al., 2000). Using AFNI's 3dDeconvolve tool, a general linear model (GLM) was then applied to each participant's co-registered functional images and movement time-series data. The GLM

analysis incorporated covariates accounting for linear, quadratic, cubic, and quartic drift, six motion parameters, eight physiological noise regressors, and the reference functions. The GLM was performed on a slice-by-slice basis with slices re-assembled into a 3D map. The physiological regressors had a differential correction depending on slice to account for the differential effects of physiological motion depending on brain location.

Spatial smoothing was not used for the ICA portion of the analysis, per recommendations by the developers of FSL, as such smoothing will lead to lesser detail in the component extraction and causes peak activation focus to be displaced. A high pass filter was also not be applied, again based on the FSL developers' recommendations, as this is only recommended for resting-state network extraction, not for task based component extraction (Beckmann & Smith, 2004; Jenkinson et al., 2012b).

Analysis

Preprocessing

Initially, independent component analysis (ICA) was used to extract timeseries data from relevant brain networks in HC and SZ participants. ICA is a statistical method used to separate signal into its additive components, or blind source separation (Bell & Sejnowski, 1995). This technique was chosen in order to identify the network ROIs from all participants using a data driven technique. Probabilistic ICA analysis was conducted using Multivariate Exploratory Linear Optimized Decomposition into Independent Components (MELODIC) in FSL to extract brain networks and their time course data (Beckmann & Smith, 2004). Unfortunately, the ROIs extracted were more

representative of nodes within networks without clear parcellation rather than full networks. For example, the components that were picked out were either too granular or too large and not constrained the networks of interest (Figures 1-2). Therefore, the brain components that were extracted using MELODIC were not used to create ROIs for use with GLM. Instead, pre-existing masks were constructed using Functional Imaging in Neuropsychiatric Disorders (FIND) lab functional brain network ROIs (Shirer et al., 2012). Sub-networks for CEN are the right CEN (rCEN), and left CEN (lCEN). Subnetworks for the SN are the anterior SN (aSN) and the posterior SN (pSN). Sub-networks for the DMN are the dorsal DMN (dDMN) and the ventral DMN (vDMN). FIND lab masks were also combined into single network ROIs from smaller component ROIs using AFNI's 3dcalc function (for example, the right and left executive control network ROIs were combined into a single executive control network ROI to better match the literature on large scale brain network ROIs). These masks were then resampled using AFNI's 3dresample function to match fMRI voxel resolution (2.4 mm isotropic) and were then ready to be used for the ROI analysis.

Aim 1 Analyses

Hypothesis 1 relied on linear mixed-effects models using the lme4 package for R (Bates et al., 2015). Mental workload was operationalized as discriminability (d') from an equal variance signal detection-item response model (Thomas et al., 2018) estimated within each level of N-Back load. That is, each participant had five estimates of d': d' at 1-back, d' at 2-back, d' at 3-back, d' at 4-back, and d' at 5-back. Our lab has previously shown that this type of analysis—referred to as conditional performance analysis—provides more accurate and interpretable estimates of mental workload using fMRI data

(Thomas et al., 2021). Blood Oxygen-Level Dependent (BOLD) activity within each ROI was regressed onto group (dummy coded), mental workload (contrast polynomial coded with linear and quadradic terms), and the group by mental workload interaction. Random intercepts were included in the models as well. Inferential tests were two-sided at $p < 0.05$. Hierarchical regression was used to determine which fixed effects to include in each model for each ROI. Model 1 only contained the intercept. Model 2 contained the intercept and group fixed effect. Model 3 contained the intercept, group, and linear d' fixed effects. Model 4 contained the intercept, group, linear d', and quadratic d' fixed effects. Model 5 contained the intercept, group, linear d', quadratic d', and group by linear d' interaction fixed effects. And, finally, model 6 contained the intercept, group, linear d', and quadratic d', group by linear d' interaction, and group by quadratic d' interaction fixed effects. Models were then compared for each network and all sub-networks using the Akaike information criterion (AIC), Bayesian information criterion (BIC), and chi-squared difference test ($\Delta\chi 2$). AIC is an estimator of prediction error making lower values point to a better fitting model. BIC is related to AIC, as both use likelihood functions, but BIC uses Bayesian methods. For BIC lower values indicate better model fit as well. Finally, $\Delta\chi 2$ is an indicator of whether the current model is significantly different (better fit) than the one before, so if significant the more complex model is needed, as it provides a better fit to the data.

Aim 2 Analyses

Causal relationships between networks were examined using dynamic causal modeling (DCM). DCM was chosen as it is a technique specifically developed for neuroimaging to compare models based on theory by quantifying how well they fit the

data using Bayesian model selection after modeling the neuronal response from the BOLD signal using a series of differential equations (Friston et al., 2003).

Images from AFNI were converted to Neuroimaging Informatics Technology Initiative (NIfTI-1) format for use in the DCM pipeline using AFNIs '3dAFNItoNIFTI' for all scans and all participants. Four dimensional NIfTI-1 fMRI images were then converted to multiple three-dimensional images (one per full scan repetition or 512) per scan per participant using the FMRIB Software Library (FSL-6) function 'fslsplit'. Statistical Parametric Mapping (SPM12; Ver. 12) in conjunction with Matlab, a common DCM pipeline, was used to perform DCM analyses (Ashburner et al., 2014). Models were constructed and selected based on the aforementioned triple network model of task engagement as well as previous research on network dynamics in schizophrenia (Calhoun, 2009; Dauvermann et al., 2014; Diaconescu et al., 2011; Hare et al., 2019; Jeong & Kubicki, 2010; Mc Glanaghy et al., 2021; Menon, 2011). These task load input models represent the three direct inputs to each of the three networks in the triple network model (Figure 1).

fMRI model specification and estimation was set up using seconds for units of design, and an interscan interval of 0.8 seconds (repetition time from the scanner), microtime resolution and microtime onset were left at default values (16 and 8 respectively). Onsets were then specified according to the task block onsets in seconds (10, 90, 170, 250, 330s) accounting for 60s task block durations and a 20s inter-task interval. Parametric modulations were set up for linear effects and quadratic effects (polynomial expansion of 2nd order) of load using task order for positioning of load in the design matrix as follows depending on condition block (3 1 5 2 4, or 5 3 2 4 1, or 2 4 1

3 5). The global masking threshold was left at the default of 0.8. Then, an omnibus F-contrast was set up using a 3x3 weight matrix (for intercept, linear, and quadratic conditions). Using the model estimation and F-contrast, time series data were extracted from network ROIs (from FIND lab) using a threshold of 1 for all activity. Extracted time series data and specified models were then used (specified in matrix form with columns specifying connection source, and row specifying targets) for random effects Bayesian model comparison for individual then group. The best fitting model was determined by model expected probability (probability of the given model fitting for a random subject), model exceedance probability (probability that one model is more likely than any others), and the probability of equal model frequencies (probability that all models have the same frequency in the group).

RESULTS

Aim 1 Results

Participants did not differ in age, race, ethnicity, gender, or parent's education in years (Table 1). They did differ in years of education and WRAT scores, which is common for HC to SZ samples. Chlorpromazine dose, SAPS, and SANS were not applicable to the HC group.

Central Executive Network

The model that included group, linear, and quadratic terms as regressors was the best model for the bilateral CEN ROI, the rCEN ROI, and the lCEN ROI (Table 2). The CEN shows a significant negative quadratic effect for mental workload and no significant group effects (Table 5). Predictions for this model, shown in Figure 2, show that patterns of brain activity are greatest for modest levels of mental workload. Additionally, there is little separation between HC and SZ in model predictions.

Salience Network

The model that included group, linear, and quadratic terms as regressors was the best model for the combined SN ROI, aSN ROI, and for the pSN ROI. For the combined SN ROI and the pSN ROI there was a significant group effect (Table 3). Additionally, there were significant quadratic effects for all three SN ROIs (Table 6). Predictions for this model, shown in Figure 2, show that patterns of brain activity are greatest for modest levels of mental workload in the combined SN ROI and aSN ROI with little separation between HC and SZ. In contrast, the pSN shows larger separation between HC and SZ with SZ showing greater activity.

Default Mode Network

The model that included group only was the best model for the combined DMN ROI and the vDMN ROI (Table 4). The model that contained group and linear effects was the best model for the dDMN ROI. Significant effects for group were found in the combined DMN ROI, dDMN ROI, and vDMN ROI. Additionally, a significant linear effect was found in the dDMN ROI. Predictions for these models, shown in Figure 2, show separation between HC and SZ for all DMN ROIs and a linear trend can be seen in the dDMN ROI depicting brain activity increasing with lower levels of mental workload (higher d'). It is also notable that the vDMN ROI show more of a quadratic curve for HC in the vDMN ROI.

Aim 2 Results

For the exploratory aim we found that there are group differences in which network is affected by task load. Specifically, we found that task load seems to act as an input on CEN in HC while acting as an input on SN in SZ (Figure 3). It should be noted, however, that the probabilities of equal model frequencies are high for both HC and SZ. In SZ that probability is very high.

DISCUSSION

This paper set out to examine large-scale brain network differences between HC and SZ as it pertains to mental workload. Specifically, the first aim of this project was to compare patterns of activity in the CEN, SN, and DMN between HC and SZ with the hypothesis that SZ would show less mental workload modulation of these networks. For mental workload, we found that overall activity was higher in the SN, pSN, DMN, dDMN, and vDMN, though the patterns of activity (e.g. linear or quadratic) were largely similar between groups.

For the CEN ROIs, there were no significant differences between HC and SZ. That is, peak brain activation was observed at modest levels of mental workload. At highest and lowest levels of mental workload, activity was lower, showing an overall inverted-U or quadratic curve. This implies that when the task is easier for a participant, they do not show as much brain activity as they find the task less challenging, whereas when the task is harder for the participant, they find the task more challenging, and engagement may be less effortful. The peak at the modest mental workload level indicated that the challenge matches ability. Such a finding was not unexpected as it is in line with previous research (Thomas et al., 2021).

For the SN ROIs, observations for the aSN were similar to that of the CEN ROIs. Whereas for the combined SN and pSN, the shape of the brain activity as it related to mental workload was similar in HC and SZ, but the overall activity level in SZ was higher. This seems to imply that the SN and pSN are having a harder time performing their role in mediation between the CEN and DMN and may be giving excess attention to internal experiences (Wotruba et al., 2014). Alternately, it could suggest that there is

a breakdown of the link between the CEN and the SN in SZ (Manoliu et al., 2014; Palaniyappan et al., 2013).

For the DMN ROIs, the combined DMN differences between HC and SZ in that SZ showed higher activity overall. There was also a slight increase in DMN activity as mental workload decreased for both HC and SZ. In the dDMN, activity for SZ was also significantly higher, and as mental workload decreases vDMN activity increases for both HC and SZ. In the vDMN overall activity was also higher for SZ, and there was a significant inverted-U or quadratic curve. That this implies that the idea of the triple network model where the CEN and DMN show inverse activity from one another may not take into account non-linear relationship with task load. For SZ, the DMN activity seems entirely linear, where the CEN activity shows the expected inverted-U or negative quadratic curve. In the vDMN, HC show an inverted-U or negative quadratic curve, so both the CEN and vDMN show the same curve. More research is needed both to confirm these findings and investigate this phenomenon. These findings do suppose the idea that impaired DMN suppression is present in SZ (Jeong & Kubicki, 2010; Zhou et al., 2016).

Our hypothesis was partially supported by these group differences, as there were differences in the pSN, DMN, dDMN, and vDMN but not in the others. There were no interactions that we were able to detect with this sample size, though the plots could indicate that there might be some with a small effect size. It is also of note that the DMN showed a linear curve instead of the quadratic U curve that would represent the inverse activity pattern from the CEN, as expected from the triple network model. These findings confirm that SZs are inefficient at suppressing the DMN (Zhou et al., 2016) and

show more activity in the SN and pSN to achieve the same level of same task performance as HCs. Interpreting the relationship between fMRI BOLD signal and neuronal activity is outside of the scope of this paper.

Additionally, our exploratory aim sought to examine N-back load input difference models using DCM. We found that task-load acts as an input to CEN in HC and in SZ task-load acts as an input to the SN using random effects Bayesian model selection. This was surprising, and possibly indicates that task load acts as an input to the CEN in HC to allow the CEN to direct load-based information to the SN, which in turn moderates the CEN and DMN in accordance with the triple network model (Menon, 2011). Task load acting as an input to the SN in SZ could have a number of different interpretations. One possibility is that the SN is not responding properly in SZ, and thus interpreting N-back load differently than the CEN. This would be in line with current literature that shows that insula (a primary SN node) dysfunction and aberrant salience network activity have been noted in SZ (Manoliu et al., 2014; Palaniyappan & Liddle, 2012; Wotruba et al., 2014). A second possibility, related to the CEN itself being disrupted in SZ (Chen et al., 2016), is that the CEN is dysfunctional in SZ and is unable to redirect the load information properly. If this is true, it could be that the SN somehow compensates for poor executive control functions in patients. It is also possible that the DMN is not being properly suppressed by either the CEN or SN (Zhou et al., 2016), and thus overactivity in the DMN is causing this input discrepancy. Clearly, more research is needed.

As mentioned earlier, current treatment options for SZ are largely limited, pharmacological in nature, and focused on controlling positive symptoms (Kane &

Marder, 1993; Keepers et al., 2020). Our understanding of functional and effective connectivity in SZ could lead to better or alternate treatments. Potential ramifications of these findings are numerous.

For the CEN, some previous findings have demonstrated either hypoactivity (Glahn et al., 2005) or hyperactivity (Brown & Thompson, 2010) in the dorsolateral prefrontal cortex (the primary hub node of the CEN), so there is some disagreement between these findings. This study and more recent findings suggest that, when taking mental workload into effect, there may be less of a difference to HC than previously thought, suggesting that the CEN may not be a great target for treatment (Thomas et al., 2021).

In the SN, this study found hyperactivity in the combined SN and pSN. This is in line with other findings suggesting inefficacies in the SN (Chen et al., 2016; Manoliu et al., 2014; Palaniyappan et al., 2013). These findings, combined with this and other studies' support of a lack of suppression of the DMN, suggest that network relationship between the SN and the DMN could be an idea target for treatment.

It has been demonstrated that one can alter large-scale brain network connectivity pharmacologically (Grady et al., 2013), through neural stimulation using transcranial direct current stimulation or transcranial magnetic stimulation (Muldoon et al., 2016), and through mindfulness meditation (Fam et al., 2020). Future research could use these methods to focus on treating hyperactivity and inefficacies between the SN and DMN networks.

Limitations

Results of this study should be interpreted in light of its limitations. First, the results could only apply to the N-back task or working memory tasks more broadly. Additionally, research is needed using different cognitive tasks and domains of cognition. Second, the sample was modest in size. A larger sample size may reveal more subtle effects than those reported here. Third, SZ and HC could not be randomized, as one cannot randomize disease. Therefore, any condition uniquely related to having schizophrenia is potentially a confound. Fourth, although effect sizes are reported for all inferential tests, familywise error corrections were not applied to the results, which could lead to Type I errors. Lastly, network-based volumes of interest (VOI) have not been used much in DCM. The intrinsic connections of major networks are more complicated than simpler nodal based VOIs (Suárez et al., 2020), so this could potentially cloud the model comparison. A direct comparison of more nodal VOI versus full network VOI should be conducted. Other methods that are more general could also be employed to test this method's validity (SEM, Granger causality, etc.).

Conclusion

It is of note that, though SZ display the same activity pattern as it relates to mental workload in network activation as HC, overall activity is higher in the pSN and DMN. This is not unexpected, given the cognitive deficits in SZ. The linear activation of the DMN in mental workload in both HC and SZ warrants more research as well as the differences in causal input relationships between N-back load and these networks as this could suggest that there are potentially fundamental differences in how HC and SZ process task load. Methodological comparison studies might focus on ICA extraction versus network ROI mask extraction (for post-hoc analysis) as well as comparison

between network VOI and nodal-based DCM model comparison. Finally, more studies are needed to fully understand network relationships and effective connectivity in patients with schizophrenia to form a more complete picture and thus have more relevant recommendations for treatment.

Table 1. Demographics and clinical characteristics

	HCs	SZs	*p* HCs vs. SZs
Sample size	25	27	-
Age	40.60 (9.38)	43.26 (9.59)	0.32
Age Range	23-54	21-58	-
Sex: Male	16 (65%)	18 (67%)	>.999
Hispanic	5 (20%)	8 (30%)	0.53
Race	-	-	0.37
American Indian / Alaskan Native	0 (0%)	1 (4%)	-
Asian	4 (16%)	3 (11%)	-
Black or African American	2 (8%)	6 (22%)	-
More than one race	5 (20%)	2 (7%)	-
White	14 (56%)	15 (56%)	-
Education	15.80 (2.06)	12.70 (2.15)	<.001
Parents' education	13.92 (3.56)	12.67 (3.25)	0.19
WRAT reading score	104.36 (10.98)	96.00 (10.87)	0.01
Chlorpromazine equivalent doses	-	482.61 (462.83)	-
SAPS	-	21.48 (9.90)	-
SANS	-	6.59 (4.11)	-

Note: HC = Healthy Controls. SZs = Patients diagnosed with schizophrenia. Means reported for continuous variables with percentages and counts for discreet variables. Groups were compared using regression for continuous variables and Fisher's exact test for categorical variables. Education is in years completed. SANS = Scale for the Assessment of Negative Symptoms reported as total global rating scores. SAPS = Scale for the Assessment of Positive Symptoms reported as total global rating scores; WRAT = Wide Range Achievement Test.

Table 2. CEN model comparison statistics

CEN	npar	AIC	BIC	*Δχ2*	df	*p*
Intercept	3	234.88	247.64			
Group	4	236.49	253.50	0.394	1	0.5301
GrpLinear	5	238.36	259.63	0.123	1	0.7263
GrpLinQuad	6	232.89	258.41	7.473	1	0.0063 **
Int1	7	232.96	262.74	1.926	1	0.1652
Full	8	234.88	268.92	0.078	1	0.7804

rCEN	npar	AIC	BIC	*Δχ2*	df	*p*
Intercept	3	357.70	370.46			
Group	4	359.48	376.49	0.220	1	0.6393
GrpLinear	5	361.41	382.68	0.065	1	0.7983
GrpLinQuad	6	356.11	381.63	7.303	1	0.0069 **
Int1	7	356.05	385.83	2.053	1	0.1519
Full	8	357.92	391.95	0.137	1	0.7112

lCEN	npar	AIC	BIC	*Δχ2*	df	*p*
Intercept	3	167.23	180.00			
Group	4	168.68	185.69	0.558	1	0.4553
GrpLinear	5	170.43	191.70	0.246	1	0.6203
GrpLinQuad	6	165.99	191.52	6.437	1	0.0112 *
Int1	7	166.81	196.59	1.181	1	0.2772
Full	8	168.79	202.82	0.023	1	0.8784

Note: The above are model fit statistic using analysis of variance (ANOVA) comparing all hierarchical models. All models regressed onto centered BOLD signal for the given network. Intercept – Model with only the intercept. Group – Model with intercept and group. GrpLinear = Model with intercept, group, and linear mental workload. GrpLinQuad – Model with intercept, group, linear mental workload, and quadratic mental workload. Int1 - Model with intercept, group, linear mental workload, quadratic mental workload, and group by linear interaction. Full - Model with intercept, group, linear mental workload, quadratic mental workload, group by linear interaction, and group by quadratic interaction. Npar – number of parameters in the model. AIC – Akaike Information Criteria. BIC – Bayesian Information Criteria. *Δχ2* – Chi-squared. Df – Degrees of freedom. p – p-value.

Table 3. SN model comparison statistics

SN	npar	AIC	BIC	$\Delta\chi 2$	df	*p*
Intercept	3	-20.91	-8.15			
Group	4	-22.15	-5.14	3.242	1	0.0718 .
GrpLinear	5	-20.20	1.07	0.045	1	0.8321
GrpLinQuad	6	-24.28	1.24	6.085	1	0.0136 *
Int1	7	-23.35	6.42	1.070	1	0.3009
Full	8	-21.40	12.64	0.041	1	0.8392

aSN	npar	AIC	BIC	$\Delta\chi 2$	df	*p*
Intercept	3	-20.91	-8.15			
Group	4	24.34	41.35	<0.001	1	>0.999
GrpLinear	5	26.24	47.51	0.093	1	0.7609
GrpLinQuad	6	22.62	48.14	5.627	1	0.0177 *
Int1	7	23.67	53.44	0.949	1	0.3301
Full	8	25.65	59.68	0.016	1	0.8991

pSN	npar	AIC	BIC	$\Delta\chi 2$	df	*p*
Intercept	3	67.02	79.78			
Group	4	59.37	76.39	9.645	1	0.0019 **
GrpLinear	5	60.47	81.74	0.899	1	0.3432
GrpLinQuad	6	57.62	83.14	4.854	1	0.0276 *
Int1	7	59.00	88.78	0.615	1	0.4330
Full	8	60.85	94.88	0.154	1	0.6949

Note: The above are model fit statistic using analysis of variance (ANOVA) comparing all hierarchical models. All models regressed onto centered BOLD signal for the given network. Intercept – Model with only the intercept. Group – Model with intercept and group. GrpLinear = Model with intercept, group, and linear mental workload. GrpLinQuad – Model with intercept, group, linear mental workload, and quadratic mental workload. Int1 - Model with intercept, group, linear mental workload, quadratic mental workload, and group by linear interaction. Full - Model with intercept, group, linear mental workload, quadratic mental workload, group by linear interaction, and group by quadratic interaction. Npar – number of parameters in the model. AIC – Akaike Information Criteria. BIC – Bayesian Information Criteria. $\Delta\chi 2$ – Chi-squared. Df – Degrees of freedom. p – p-value.

Table 4. DMN model comparison statistics

DMN	npar	AIC	BIC	$\Delta\chi 2$	df	*p*
Intercept	3	20.89	33.65			
Group	4	13.25	30.27	9.635	1	0.0019 **
GrpLinear	5	11.92	33.19	3.336	1	0.0678 .
GrpLinQuad	6	13.25	38.78	0.662	1	0.4157
Int1	7	15.07	44.85	0.181	1	0.6705
Full	8	15.97	50.00	1.101	1	0.2942

dDMN	npar	AIC	BIC	$\Delta\chi 2$	df	*p*
Intercept	3	94.33	107.09			
Group	4	86.52	103.53	9.812	1	0.00173 **
GrpLinear	5	80.52	101.79	7.993	1	0.00470 **
GrpLinQuad	6	82.46	107.98	0.070	1	0.7916
Int1	7	84.45	114.23	0.003	1	0.9574
Full						

vDMN	npar	AIC	BIC	$\Delta\chi 2$	df	*p*
Intercept	3	128.36	141.12			
Group	4	123.96	140.97	6.403	1	0.0114 *
GrpLinear	5	125.95	147.22	0.009	1	0.9236
GrpLinQuad	6	123.07	148.59	4.881	1	0.0272 *
Int1	7	124.06	153.83	1.012	1	0.3145
Full	8	125.14	159.17	0.912	1	0.3395

Note: The above are model fit statistic using analysis of variance (ANOVA) comparing all hierarchical models. All models regressed onto centered BOLD signal for the given network. Intercept – Model with only the intercept. Group – Model with intercept and group. GrpLinear = Model with intercept, group, and linear mental workload. GrpLinQuad – Model with intercept, group, linear mental workload, and quadratic mental workload. Int1 - Model with intercept, group, linear mental workload, quadratic mental workload, and group by linear interaction. Full - Model with intercept, group, linear mental workload, quadratic mental workload, group by linear interaction, and group by quadratic interaction. Npar – Number of parameters in the model. AIC – Akaike Information Criteria. BIC – Bayesian Information Criteria. $\Delta\chi 2$ – Chi-squared. Df – Degrees of freedom. p – p-value.

Table 5. Central Executive Network Best Model Statistics

	Central Executive Network				Right Central Executive Network				Left Central Executive Network			
	β	p	SE		β	p	SE		β	p	SE	
Intercept	0.0965	0.0061	0.0338	**	0.1351	0.0011	0.0392	**	0.0481	0.1384	0.0320	
Group	0.0372	0.4301	0.0468		0.0352	0.5202	0.0543		0.0387	0.3872	0.0443	
Mental Workload	0.0217	0.0921	0.0129	.	0.0250	0.0847	0.0145	.	0.0176	0.1454	0.0121	
Mental Workload Quad.	-0.0075	0.0061	0.0027	**	-0.0083	0.0069	0.0031	**	-0.0065	0.0105	0.0025	*

R^2 m	R^2 cond.	R2m	R2c	R2m	R2c
0.0157	0.2125	0.0143	0.2268	0.0150	0.2171

Note: Reported statistics from best fitting model for central executive network (CEN).

Table 6. Salience Network Best Model Statistics

	Salience Network				Anterior Salience Network				Posterior Salience Network			
	β	p	SE		β	p	SE		β	p	SE	
Intercept	0.0107	0.7058	0.0282		0.0890	0.0072	0.0318	**	-0.1239	<0.001	0.0320	***
Group	0.0790	0.0487	0.0391	*	0.0335	0.4500	0.0441		0.1526	0.0012	0.0444	**
Mental Workload	0.0189	0.0594	0.0100		0.0152	0.1459	0.0105		0.0241	0.0263	0.0108	*
Mental Workload Quad.	-0.0052	0.0142	0.0021	*	-0.0052	0.0185	0.0022	*	-0.0050	0.0281	0.0023	*
	R2m	R2c			R2m	R2c			R2m	R2c		
	0.0296	0.2587			0.0119	0.2854			0.0708	0.3137		

Reported statistics from best fitting model for central executive network (CEN).

Table 7. Default Mode Network Best Model Statistics

	Default Mode Network				Dorsal Default Mode Network				Ventral Default Mode Network			
	β	p	SE		β	p	SE		β	p	SE	
Intercept	-0.2360	<0.001	0.0260	***	-0.2768	<0.001	0.0298	***	-0.1796	<0.001	0.0287	***
Group	0.1151	0.0025	0.0361	**	0.1408	0.0013	0.0414	**	0.1081	0.0090	0.0398	**
Mental Workload	0.0138	0.0614	0.0074	.	0.0227	0.0039	0.0078	**	0.0194	0.0946	0.0116	.
Mental Workload Quad.									-0.0055	0.0264	0.0024	**

R2m	R2c
0.0489	0.2200

R2m	R2c
0.0650	0.2648

R2m	R2c
0.0390	0.2047

Note: Reported statistics from best fitting model for central executive network (CEN).

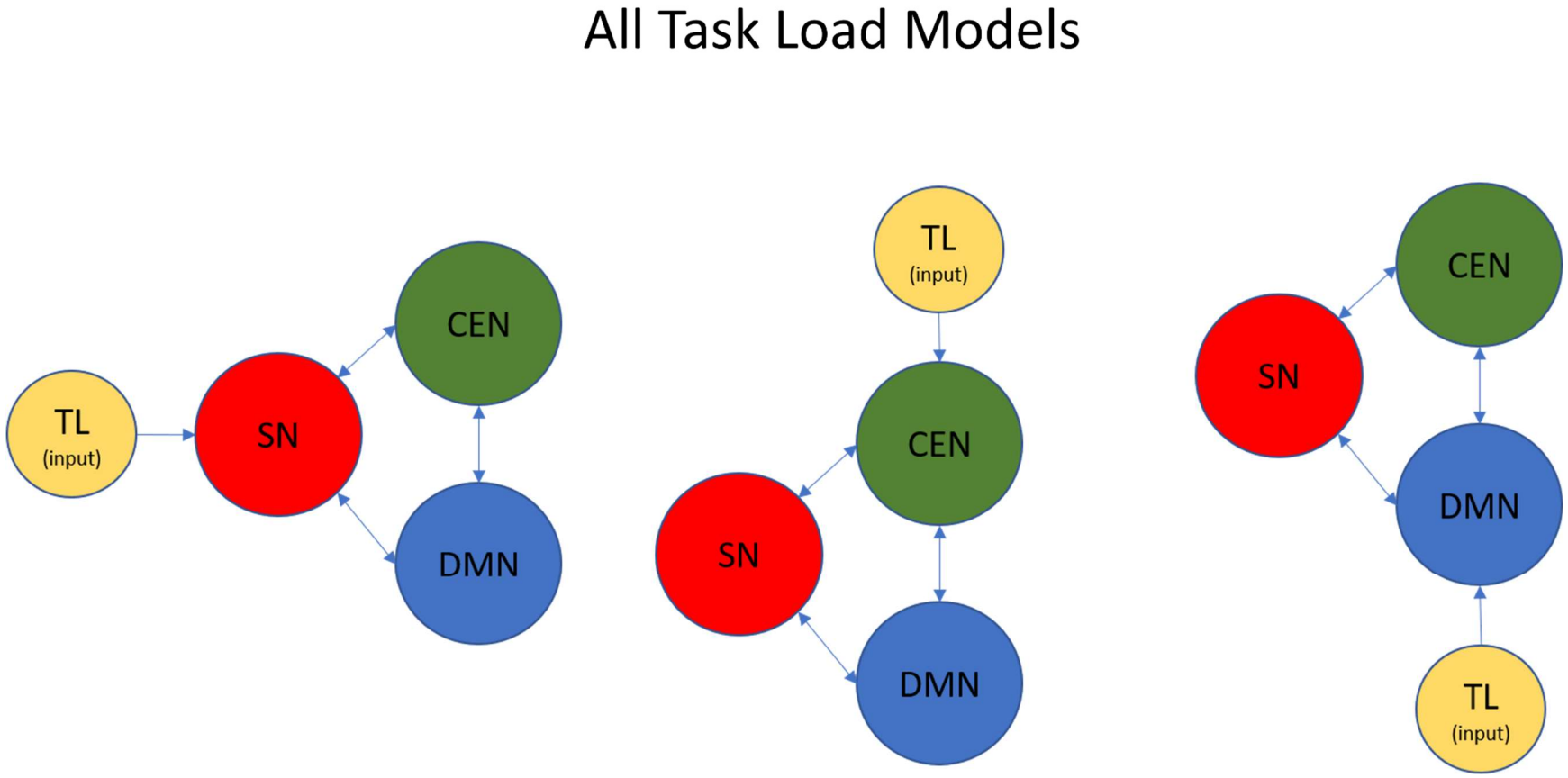

Figure 1: All Task Load input models for DCM analysis.

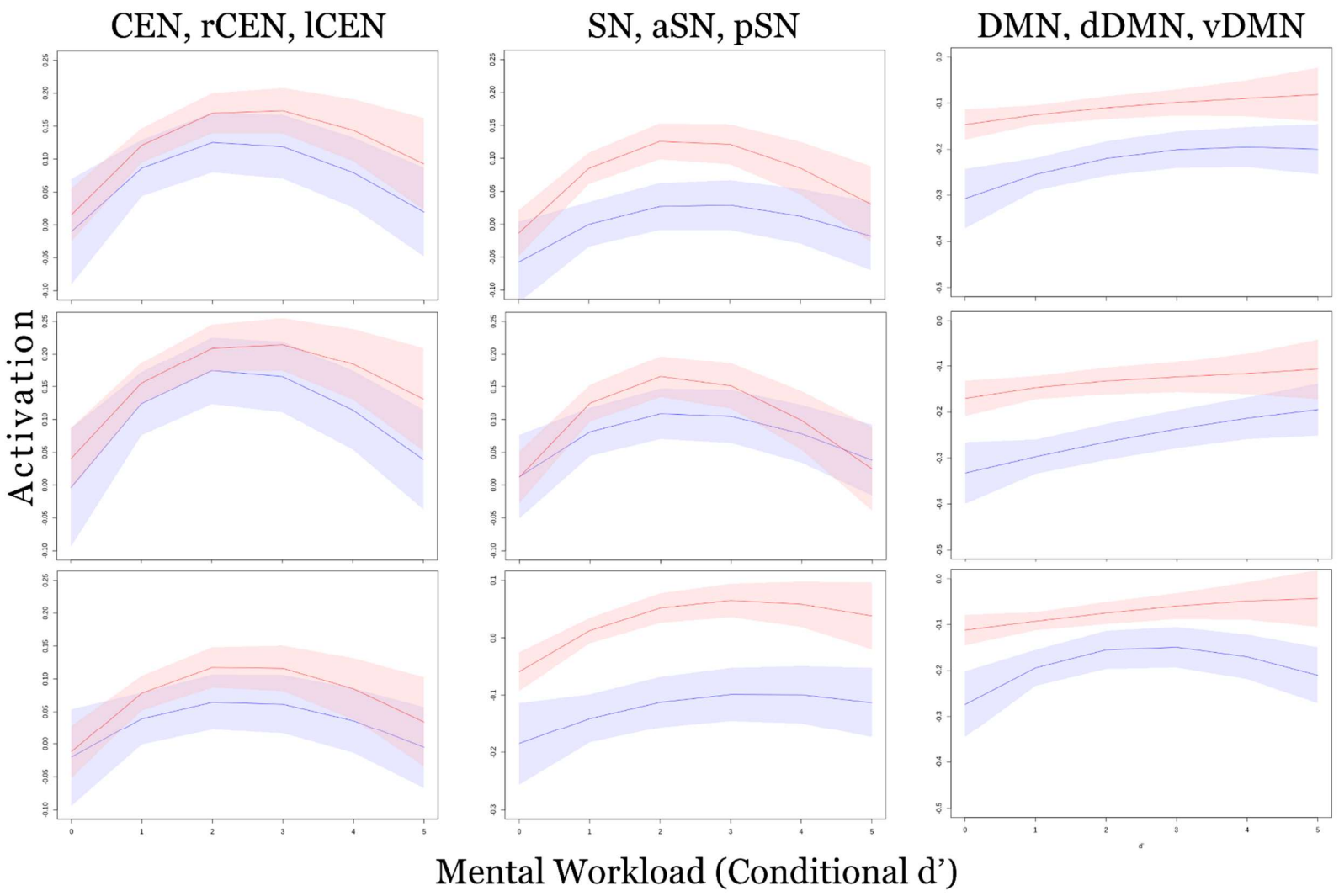

Figure 2: Model predictions for best fitting linear mixed model regression. Y-axis - Network Blood Oxygen-Level Dependent (BOLD) Activity shown as a function of conditional performance. X-axis – Mental workload as discriminability (d').

HC

SZ

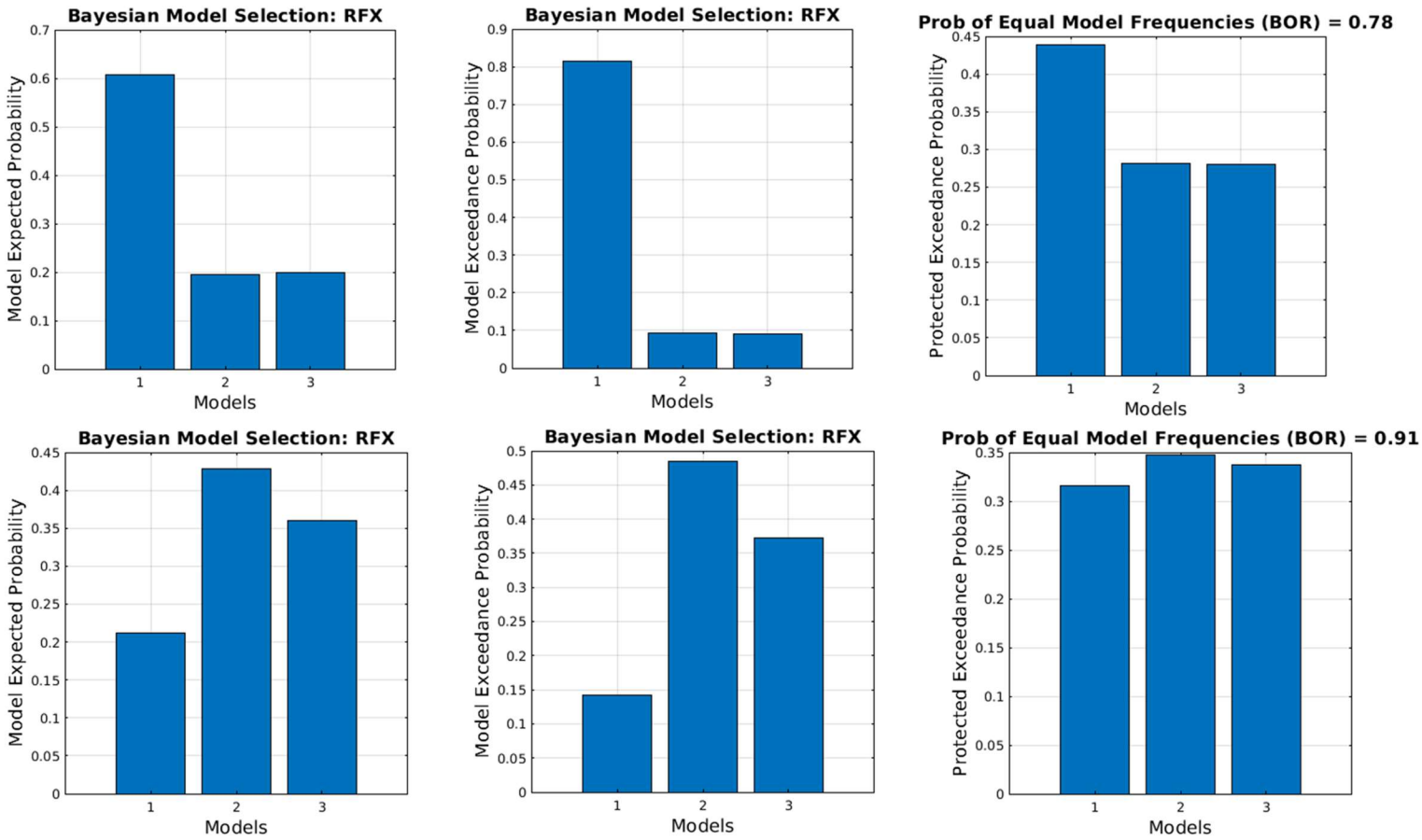

Figure 3: Random effects (RFX) Bayesian model selection from dynamic causal modeling (DCM). On the y-axis, column 1 is the model expected probability (probability of the given model fitting for a random subject), column 2 is the model exceedance probability (probability that one model is more likely than any others), column 3 is the probability that all models have the same frequency in the group.

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