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Five Negative Symptom Domains are Differentially Associated with Resting State Amplitude of Low Frequency Fluctuations in Schizophrenia

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EJC, AGM, and TGMvE created the first draft of the manuscript. BG, BMA and TGMvE conducted the imaging and statistical analyses. All other co-authors critically reviewed the manuscript and provided comments.

Conflict of interest

Dr. Daniel H. Mathalon consulted for Neurocrine Biosciences, Gilgamesh Pharmaceuticals, and Recognify Life Sciences, and served on a data safety monitoring/advisory board for Neurocrine Biosciences. The other authors have no conflict of interest to report.

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Abstract

This study examined associations between resting-state amplitude of low frequency fluctuations (ALFF) and negative symptoms represented by total scores, second-order dimension (motivation and pleasure, expressivity), and first-order domain (anhedonia, avolition, asociality, alogia, blunted affect) factor scores in schizophrenia (n=57). Total negative symptom scores showed positive associations with ALFF in temporal and frontal brain regions. Negative symptom domain scores showed predominantly stronger associations with regional ALFF compared to total scores, suggesting domain scores may better map to neural signatures than total scores. Improving our understanding of the neuropathology underlying negative symptoms may aid in addressing this unmet therapeutic need in schizophrenia.

Keywords

ALFF; Negative Symptoms; Avolition

1. Introduction

The clinical course, prognosis, and quality of life of individuals with schizophrenia are associated with the severity of negative symptoms which are defined as deficiencies in the areas of motivation, emotion, and communication (Green et al., 2012). An improved understanding of the underlying neuropathology of negative symptoms may aid in developing better treatments for this unmet therapeutic need (Rabinowitz et al., 2012; Robertson et al., 2014).

Studies of the pathophysiology underlying the broad construct of negative symptoms have failed to show consistent findings, ostensibly due to heterogeneity between different negative symptom constructs (Galderisi et al., 2018). Negative symptoms form a hierarchical structure with two second-order dimensions [motivation and pleasure (MAP), diminished expression (EXP)] and five first-order domains (anhedonia, avolition, and asociality, blunted affect and alogia) (Strauss et al., 2019a, 2019b, 2018). We assert that examining associations between these negative symptom dimensions and domains and brain imaging measures will be informative regarding their pathophysiology, advancing efforts to develop more refined treatments targeting specific symptom domains.

Abnormalities in resting-state brain activity are robust in schizophrenia. Amplitude of low frequency fluctuations (ALFF)—a resting-state brain activity measure obtained from functional magnetic resonance imaging (fMRI) data—is computed as the average square root of the power spectrum within a frequency band at each brain voxel, yielding a measure

of the average amplitude of blood oxygen level dependent (BOLD) signal fluctuations over time. It can also be normalized by the power of the entire frequency range resulting in fractional ALFF (fALFF). ALFF is sensitive to baseline cerebral blood flow and reflects spontaneous and intrinsic neural activity (Zhou et al., 2010).

A meta-analysis found that ALFF is lower in somatosensory cortex, posterior parietal cortex, and occipital cortex, and is higher in bilateral striatum, medial temporal cortex, and medial prefrontal cortex in schizophrenia compared to controls (Xu et al., 2015). There is also evidence of associations between ALFF and hallucinations (Hare et al., 2018, 2017). However, associations between regional ALFF and negative symptoms remain to be determined.

One study found that deficit schizophrenia (DS), characterized by primary and persistent negative symptoms, compared to non-deficit schizophrenia (NDS) exhibited lower fALFF in the left insula and frontotemporal cortex, bilateral insula, and anterior cingulate gyrus, and greater fALFF in the bilateral visual cortex (Zhou et al., 2019). Another found a positive association between right putamen ALFF and a negative association between left cerebellum ALFF and total negative symptom severity in DS but not NDS (Li et al., 2017). However, these studies did not examine associations between ALFF and negative symptom subdomains. This study examined, to our knowledge for the first time, the associations between ALFF and dimensions and domains of negative symptoms.

2. Methods

Eyes-closed rsfMRI data (echo planar imaging with TE/TR/FA/slices/frames/voxel size/gap = 30 ms/2 s/77°/32/162/3.4×3.4×4 mm/1 mm) was obtained from 57 individuals with schizophrenia (44 males, 32.7±11.0 age in years, 20.7±6.9 age at onset, 12.1±9.0 duration of illness in years, and CPZ dose equivalent of 378±339), who participated in the Function Biomedical Informatics Research Network (FBIRN), using an rsfMRI analysis pipeline developed by the Enhancing Neuro Imaging Genetics through Meta-Analysis (ENIGMA) consortium (Adhikari et al., 2019, 2018).

Mean±SD scores for clinical measures were 56.5±13.7 for PANSS (Positive and Negative Syndrome Scale) Total, 14.9±4.9 for PANSS Positive, 13.6±5.3 for PANSS Negative, 15.9±15.4 for SAPS (Scale for the Assessment of Positive Symptoms) Total, and 18.4±12.5 for SANS (Scale for the Assessment of Negative Symptoms) Total. We extracted mean ALFF from 68 (34 left/34 right hemisphere) Desikan-Killiany atlas cortical regions obtained using FreeSurfer (Fischl, 2012). Exploratory regression analyses examined associations (partial Pearson's r) between regional ALFF and total negative symptom, MAP and EXP dimension (Khan et al., 2017; Strauss et al., 2018), and anhedonia, asociality, avolition, blunted affect, and alogia domain scores derived from the SANS (Strauss et al., 2018) and the PANSS (Khan et al., 2017), while statistically controlling for age, gender and scanner/site (R^2 's lm). We considered all $|r\text{-values}| > 0.266$ (critical r -value, $df=55$, $p<0.05$, two-tailed), without correction for multiple comparison, as regions of interest (ROIs) for exploration in future work on larger multicenter samples. We conducted spin-tests ($n=1,000$

permutations) to determine similarities of correlation patterns between ALFF and symptoms (Alexander-Bloch et al., 2018).

3. Results

ALFF in bilateral entorhinal and inferior temporal, left lateral orbital, and right fusiform, insula, medial orbitofrontal, middle temporal, pars triangularis, postcentral, and precentral gyri were significantly correlated with SANS Total (Table 1). Among these 12 regions, nine showed significant associations with MAP and two with the EXP. Among the nine regions associated with MAP, three, four, and eight were significantly associated with anhedonia, asociality, and avolition, respectively. Of the two regions associated with EXP, one was associated with alogia, and both were associated with blunted affect (Table 1, underlined correlations).

Nine of the 12 regions that showed positive associations with SANS Total also showed positive associations with PANSS Negative. Four of the nine regions that showed positive associations with SANS MAP also showed positive associations with PANSS MAP, and both regions that showed positive associations with SANS EXP also showed positive associations with PANSS EXP (Table 1, underlined correlations).

Importantly, most of the correlations with first-order domains (e.g., SANS avolition), were higher than the broader second-order dimensions (e.g., SANS MAP), which were higher than global total scores (e.g., SANS Total).

Finally, the relationships between correlation patterns of ALFF and symptoms were: $r(\text{PANSS TOT, SANS TOT})=0.84$, $r(\text{PANSS EXP, SANS EXP})=0.96$, $r(\text{PANSS MAP, SANS MAP})=0.97$, $r(\text{PANSS EXP, PANSS MAP})=0.62$, and $r(\text{SANS EXP, SANS MAP})=0.55$; all $p\text{-spin} < 0.001$.

4. Discussion

This study explored associations between ALFF and negative symptom second-order dimensions and first-order domains. We found significant associations between frontal and temporal lobe ALFF and negative symptom severity. For the SANS, we found a larger number of significant associations between ALFF and MAP than between ALFF and EXP. For the PANSS, we found a larger number of significant associations between ALFF and EXP than between ALFF and MAP. The relationships between correlation patterns of ALFF and symptoms were higher within (EXP or MAP between PANSS/SANS) than between domains (EXP and MAP within PANSS/SANS) suggestive of different regional mapping between ALFF and EXP/MAP. While future studies should corroborate these findings, they suggest that SANS items may better reflect the MAP dimension, while PANSS items better reflect the EXP dimension.

Among the MAP subdomains, avolition exhibited the strongest association with ALFF. Moreover, most of the associations with first-order domains (e.g., avolition), were stronger than for second-order dimensions (e.g., MAP), which were stronger than for total scores, suggesting that refined symptom domain scores may better map onto some imaging

phenotypes than total negative symptom scores. Notably, a recent study showed that the MAP dimension and its subdomains (avolition, anhedonia, asociality) had similar associations with ventral striatum activation during reward anticipation (Kaliuzhna et al., 2021). While these findings may suggest limited added value of deconstructing the MAP dimension into its subdomains when examining relationships with brain imaging measures, they may also support the hypothesis that the ventral striatum is involved in all three subdomains (Strauss et al., 2019a). This study represents a first step in advancing our understanding of the pathophysiology of negative symptoms using ALFF, and we plan to generate more robust and replicable findings by conducting ENIGMA schizophrenia working group resting-state meta-analysis employing Collaborative Informatics and Neuroimaging Suite Toolkit for Anonymous Computation (COINSTAC; <http://coinstac.trendscenter.org>) framework (Ming et al., 2017).

5. Conclusion

The severity of negative symptoms is positively associated with larger amplitude spontaneous BOLD signal fluctuations in frontal and temporal lobe regions. The SANS may be more sensitive to measuring MAP, while the PANSS may be more sensitive to measuring EXP. MAP associations appear predominantly driven by avolition as compared to anhedonia and asociality. Finally, the strongest, observed associations for first-order domain scores suggest that they may represent more homogeneous constructs, that better map onto imaging phenotypes than total negative symptom scores, and may serve as separate treatment targets.

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Table 1.

Significant associations between amplitude of low frequency fluctuations (ALFF) and symptom domain factor scores based on the scale for the assessment of negative symptoms (SANS) and positive and negative syndrome scale (PANSS).

	SANS Total			SANS MAP			SANS EXP			SANS Anhedonia			SANS Asociality			SANS Avolition			SANS Alogia			SANS Blunted Affect			PANSS Negative			PANSS MAP			PANSS EXP				
	r	p		r	p		r	p		r	p		r	p		r	p		r	p		r	p		r	p		r	p		r	p			
Left entorhinal	0.294	0.043														0.286	0.049																		
Left frontal pole			-0.288	0.047						-0.327	0.023																								
Left fusiform			0.298	0.040									0.348	0.015																					
Left inferior temporal	0.413	0.004	<u>0.531</u>	<0.001						<u>0.451</u>	0.001	<u>0.380</u>	0.008	<u>0.597</u>	<0.001									<u>0.326</u>	0.024	<u>0.424</u>	0.003								
Left insula																0.373	0.009																		
Left lateral orbitofrontal	0.302	0.037	<u>0.334</u>	0.020								<u>0.305</u>	0.035	<u>0.316</u>	0.029																				
Left rostral anterior cingulate																								0.307	0.034				0.295	0.042					
Left temporal pole																														0.310	0.032				
Right entorhinal	0.304	0.036																												<u>0.305</u>	0.035				
Right fusiform	0.355	0.013	<u>0.391</u>	0.006								<u>0.294</u>	0.043	<u>0.460</u>	0.001									<u>0.293</u>	0.043	<u>0.297</u>	0.040								
Right inferior parietal																																			
Right inferior temporal	0.322	0.026	<u>0.471</u>	0.001						<u>0.374</u>	0.009	<u>0.358</u>	0.012	<u>0.510</u>	<0.001													<u>0.350</u>	0.015						
Right insula	0.318	0.028	<u>0.343</u>	0.017										<u>0.407</u>	0.004									<u>0.293</u>	0.043										
Right isthmus cingulate																																			
Right lateral occipital																0.309	0.033																		
																														</					

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	SANS Total		SANS MAP		SANS EXP		SANS Anhedonia		SANS Asociality		SANS Avolition		SANS Alogia		SANS Blunted Affect		PANSS Negative		PANSS MAP		PANSS EXP	
	r	p	r	p	r	p	r	p	r	p	r	p	r	p	r	p	r	p	r	p	r	p
Right medial orbitofrontal	0.301	0.037															<u>0.290</u>	0.046			0.306	0.034
Right middle temporal	0.295	0.042	<u>0.299</u>	0.039													<u>0.316</u>	0.028				
Right pars triangularis	0.401	0.005	<u>0.325</u>	0.024	<u>0.325</u>	0.024					<u>0.383</u>	0.007	0.285	0.050	0.311	0.031	<u>0.428</u>	0.002	<u>0.305</u>	0.035	<u>0.363</u>	0.011
Right postcentral	0.352	0.014	<u>0.332</u>	0.021			<u>0.347</u>	0.016			<u>0.290</u>	0.045					<u>0.355</u>	0.013			0.349	0.015
Right precentral	0.329	0.022	<u>0.320</u>	0.027							<u>0.356</u>	0.013					<u>0.320</u>	0.027				
Right superior temporal					0.294	0.043														0.336	0.019	
Right temporal pole																				0.297	0.040	
Right transverse temporal																				0.293	0.043	

Underlined correlations indicate consistency of PANSS Negative ratings, and second order and first order factor scores with SANS Total ratings.