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Brain Dynamics in Relation to the Activity of the Ventral Tegmental Area in Patients with Schizophrenia Studied by Resting-state fMRI

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Introduction

Schizophrenia is a complex neuropsychiatric disorder associated with abnormalities in brain function and dopamine dysregulation. The ventral tegmental area (VTA) is a crucial structure involved in dopamine production and its circuitry projects to various cortical and subcortical regions that are critical for cognitive and emotional processes(1). Additionally, alterations in synchronous activity in the cortex, which refers to the coordinated firing of neurons in different brain regions, have also been implicated in various cognitive systems(2).

Resting-state functional magnetic resonance imaging (rs-fMRI) is a non-invasive method widely used to investigate functional connectivity (FC) patterns in the brain. By measuring the degree of temporal correlation between the blood oxygen level-dependent (BOLD) signals of different brain regions during rest, rs-fMRI can provide insights into the underlying functional connections between those regions.

Given the potential role of the VTA in modulating synchronous activity in the cortex, investigating the complementary relationship between resting state networks (RSN) co-activation and VTA activity using rs-fMRI could contribute to our understanding of the pathophysiology of schizophrenia. To this end, we propose analyzing rs-fMRI data from the Human Connectome Project for Early Psychosis (HCP-EP) dataset, where schizophrenic patients are classified within the non-affective group, to examine the FC of brain regions with the activity of VTA.

Methods

Subjects: • 78 non-affective patients (age = 22 ± 3 years ; 22 females ; Naff) • 25 affective patients (age = 23 ± 3 years ; 17 females ; Aff) • 55 matched healthy controls (age = 24 ± 4 years ; 18 females ; Hc)

Preprocessing: • HCP Minimal Preprocessing Pipeline(3) • Systemic low-frequency oscillation correction of time delay range of -10 to +10 s(4) • Quality control on movements larger than 3mm and 5º

Network Identification and Synchronizations:

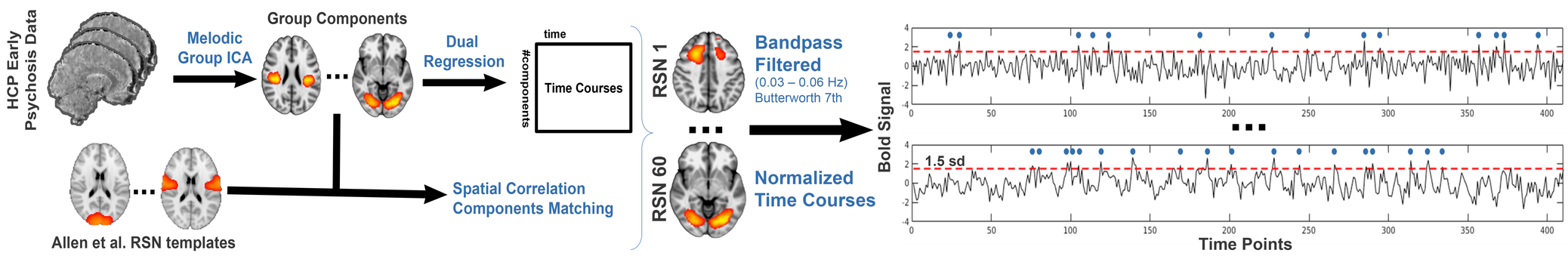

Fig. 1 – MELODIC group ICA decomposes rsfMRI data into 100 ICs, matched to Allen et al. templates for RSN identification(5). Dual regression estimates the time courses, which are bandpass filtered. Point process analysis marks events at 1.5 sd threshold crossings, and synchronous RSNs events occur simultaneously(6).

Statistical Analysis: A one-way ANOVA was conducted to investigate synchronization differences between subject groups. Subsequently, a post-hoc test using Turkey's Honestly Significant Difference was performed to identify significant differences ($p < 0.05$). The Wilcoxon signed-rank test was utilized to compare VTA activity between synchronous and off-synchronous states within each group ($p < 0.05$). Additionally, a Spearman's rank correlation analysis was conducted to investigate the relationship between the clinical and behavioral scores and the VTA activity differences ($p < 0.05$).

Results

Functional systems: In this study, we identified and categorized 60 RSNs into seven functional systems: attentional (n = 17), auditory (n = 5), basal ganglia (n = 1), default mode (n = 12), frontal (n = 6), sensorimotor (n = 13), and visual (n = 6).

Synchronization events: We examined the temporal dynamics of synchronization events in the RSNs and observed that Hc displayed a significantly higher number of in-sync time points (TPs) than patients, as shown in **Fig. 2a**. Additionally, we found that the default mode and sensorimotor networks showed stronger synchronization effects with other RSNs at the whole-dataset level (**Fig. 2b**). Furthermore, we quantified the duration of synchronous states and observed that Hc transitioned in and out of synchronization more frequently than patients. Specifically, Hc remained in synchronous states significantly longer than Naff patients (p = 10e-7).

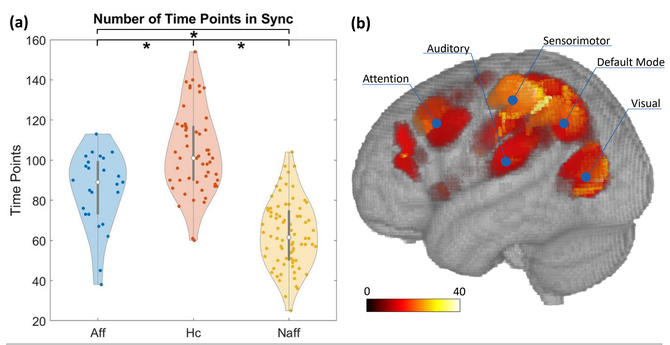

Fig. 2 – (a) Violin plots showing the distribution of the TPs in sync for each subject group. (b) Brain map showing RSNs and their group contribution differences to synchronicities.

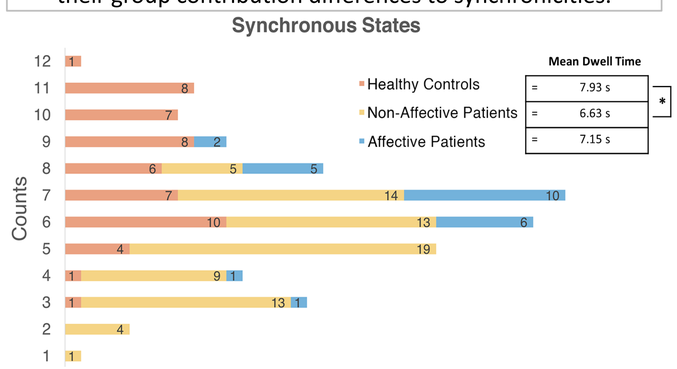

Fig. 3 – Distribution of sync states for each group with the number of subjects labeled. Mean dwell time is also displayed.

VTA Activity: Our analysis revealed that individuals with non-affective disorders showed significantly higher BOLD signal intensity in the VTA during synchronous states compared to off-synchronous states (p = 0.03), as shown in **Fig. 4**.

Cognitive Relationship: Finally, we examined the relationship between VTA activity and cognitive performance on emotion recognition tasks (**Fig 5**). In individuals with non-affective disorders, we found a negative correlation between the difference in VTA BOLD signal intensity between synchronous and off-synchronous states and performance on tasks assessing general emotion recognition and anger recognition.

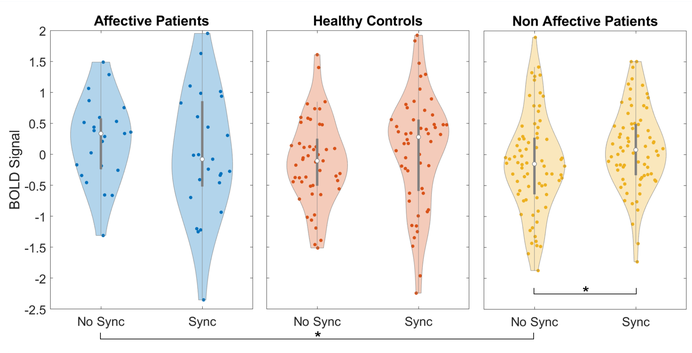

Fig. 4 – Violin plots of the distribution of the BOLD signal intensity in the VTA during in-sync and off-sync states for each group.

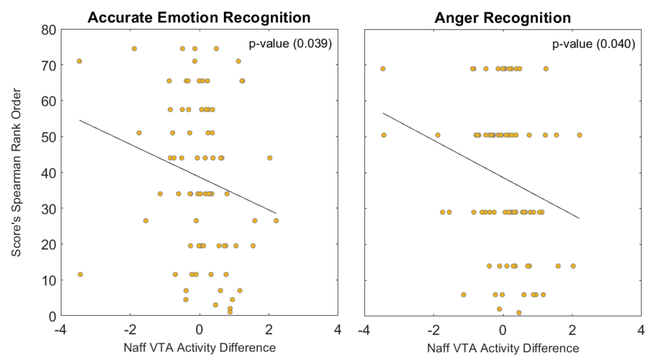

Fig. 5 – Correlation between VTA activity difference and emotion recognition scores, plotted with Spearman's rank correlation line.

Conclusion

The results provide new insights into the temporal dynamics of synchronization events and VTA activity in healthy controls and individuals with non-affective and affective disorders. We found group differences in the dynamics of synchronization events between patients and matched healthy controls. Also, we observed an association between the BOLD signal intensity of VTA in and off-synchronization periods within and across groups of subjects. However, in our study, we did not investigate the potential influence of medication on the observed differences in synch events and VTA activity between patients and healthy controls.

References

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