Learning without contingencies induces higher order asynchrony in brain networks in schizophrenia

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Introduction

- Schizophrenia (SCZ) is characterized by both cognitive and reward impairments.
- A recent circuit-based model of dysfunctional interactions between the learning and reward centers has been advanced to explain its core deficits and it notably suggests that SCZ is associated with a loss of synchrony between learning and reward circuits (Robison et al., 2019).
- Functional brain networks have structure at multiple spatial and temporal scales (Chow et al., 2019), and higher levels of disorganization may underlie failures in learning that characterized SCZ (Hütt et al., 2014).
- Here, we examined intergroup (HC vs SCZ) 4th order differences in between pairs of network pairs across an a priori connectome of cognition and reward brain circuits [(Node1 ⇆ Node2) ⇆ (Node3 ⇆ Node4)].
- The analyses were conducted on fMRI time series data acquired during a previously established associative learning paradigm (Stanley et al., 2017) with separate classes of epochs for encoding and retrieval.

Methods

- Data were collected from a total of 75 participants, 29 typical controls (age: 18-50) and 46 SCZ subjects (age:18-50).
- Multiband gradient echo EPI fMRI data acquisition was conducted on a 3T Siemens Verio system using a 12-channel volume head coil (TR:3 s, TE:24.4 ms, FOV: 192 mm × 192 mm, acquisition matrix: 96 × 96, 64 axial slices, resolution 2 mm3).
- In addition, a 3D T1-weighted anatomical MRI image was acquired (TR: 2150 ms, TI: 1100 ms, TE: 3.5 ms, flip-angle = 8°, FOV: 256 × 256 × 160 mm3, 160 axial slices, resolution = 1 mm3).
- An associative learning task was used to induce network dynamics. The task required subjects to learn associations between nine familiar objects and their locations in a two-dimensional (3 x 3) grid (Figure 1). The task alternated between Encoding, Post-Encoding Consolidation (rest), Retrieval, and Post-Retrieval Consolidation (rest) epochs (27 s per epoch) over a 13-minute acquisition period.
- During Encoding, nine familiar objects were presented in their associated grid location for naming (3 s/object). Following an instruction-free Rest interval (27 s), Retrieval consisted of cueing each grid location, requiring subjects to recall the associated object (3 s grid location), and was feedback free. Following this epoch, another instruction-free Rest interval (27 s). This cycle repeated 7 more times (8 in total).
- fMRI data were preprocessed using typical methods (SPM12) including detrending, normalization, co-registration, and motion correction.
- Time Series were extracted from eight bilateral a priori nodes (across learning and reward sub-networks) for a total of 16 nodes. The nodes were based on previous meta-analytic identification and activation loci derived from similar studies of associative memory (Diwadkar et al., 2016; Kahn and Shohamy, 2013).
- Time series from the nodes were forwarded for unidirectional functional connectivity (uFC) analysis using standard methods, computed in Matlab (Silverstein et al., 2016). Time vectors from the task separated the uFC estimates to the four epochs of interest, per each given subject.
- For each participant, uFC estimates were characterized at the 2nd order across all pairs of nodes for each of the four epochs and the resulting Pearson’s r values (correlation coefficient of the coactivity between two nodes) were transformed to Fisher’s Z Transformation for normal distribution.
- For each subject, 2nd order relationships during each of the four epochs were utilized using four unique adjacency matrices. For each matrix, the 16 nodes formed a 256-cell symmetric adjacency matrix (16 x 16), with 120 unique pairs [(16 x 16) – 16 – 2]). Each cell value represented the relationship between unique node pairs for a given subject (Figure 2a).

Methods (Cont.)

- Within each group, the values from the 2nd order matrix were submitted for 4th order analysis, creating a 4th order cross-correlation matrix for each given condition (4 total matrices per group) (Figure 2b).
- These matrices used the cognition and reward correlations (in Z scores) to find the correlations across all pairs of subnetwork pairs, resulting in 7140 ([(120 x 120) – (120 x 2)] unique 4th order pairs of pairs (correlation coefficients).
- These correlation coefficients were transformed (r’, Fisher, 1915) so that the inter-group differences in r’ (SCZ vs HC) were normalized (z) to investigate the significance of the differences between the two groups at the 4th order level (q<0.05) (Figure 2c).

Figure 1: Task Paradigm

Figure 2: Time Series and uFC Analysis

Figure 3: Connective Rings

Figure 4: Chord Frequencies Encoding vs Retrieval

Results (Cont.)

- X2 analysis was used to determine whether the evident difference in chord frequencies between the two groups (SCZ vs HC) for a given condition were significant. The 2-way X2 table used two factors: node and group (SCZ and HC), using the X2 goodness of fit test (Equation 1).
- For both Encoding and Retrieval the analyses were highly significant (Encoding: x2 = 209.59, df=15, p< 10^-4; Retrieval: x2 = 908.08, df=15, p<10^-4), indicating that both conditions evidenced significantly greater loss of 4th order synchrony in SCZ patients, relative to controls.

Discussion

Our results revealed three notable aspects:

- Even when learning without contingencies, SCZ were characterized by a preponderance of reduced 4th order synchrony between pairs of networks that span learning and reward circuits during both Encoding and Retrieval (Figures 3 and 4).
- This loss in 4th order synchrony was exacerbated during overt performance (Retrieval, Figure 3b).
- Exploratory evidence suggested some attempts to recoup this loss during post-Retrieval refractory periods.
- These results provide some guidance on interpreting how the lack of synergy between cognition and reward circuits might play out, and how this lack of synergy relates to the nature of the disorder itself (Robison et al., 2019).

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References