Characterizing insula functional connectivity in schizophrenia

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Background

- The structure of the insula is abnormal in schizophrenia\(^1\)\(^2\).
- The insula is a heterogeneous structure comprised of separate sub-regions with distinct functions and connectivity profiles, including
  - Dorsal anterior- cognitive
  - Ventral anterior- affective
  - Posterior- sensorimotor
- Functional connectivity of the insula is altered in schizophrenia\(^3\); however, few studies have taken into account sub-regions, and associations with specific clinical symptoms have not been thoroughly characterized.
- We hypothesized: schizophrenia patients would show altered functional connectivity in all insula sub-regions and tested brain-behavior relationships in schizophrenia:
  1. Hypo-connectivity of dorsal anterior insula → worse cognition
  2. Altered connectivity of ventral anterior insula → negative symptom severity
  3. Hyper-connectivity of posterior insula → positive symptom severity

Methods

<table>
<thead>
<tr>
<th>HEALTHY CONTROLS</th>
<th>SCHIZOPHRENIA</th>
<th>STATISTIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE N=196</td>
<td>N=191</td>
<td>t(385)=8.25, p&lt;.001</td>
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<tr>
<td>GENDER (M/F)*</td>
<td>120/76</td>
<td>X²=4.30, p=.038</td>
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<tr>
<td>RACE</td>
<td>139/44/11</td>
<td>X²=7.40, p=.116</td>
</tr>
<tr>
<td>WHITE/AA/OTHER</td>
<td>15.33 (2.12)</td>
<td>t(365)=8.25, p&lt;.001</td>
</tr>
<tr>
<td>PERSONAL EDUCATION*</td>
<td>13.37 (2.20)</td>
<td>t(342)=1.19, p=.235</td>
</tr>
<tr>
<td>PARENTAL EDUCATION</td>
<td>14.42 (2.35)</td>
<td>t(342)=1.19, p=.235</td>
</tr>
<tr>
<td>PANSS POSITIVE</td>
<td>17.46 (7.89)</td>
<td>--</td>
</tr>
<tr>
<td>PANSS NEGATIVE</td>
<td>15.68 (6.99)</td>
<td>--</td>
</tr>
<tr>
<td>PANSS GENERAL</td>
<td>31.33 (8.29)</td>
<td>--</td>
</tr>
<tr>
<td>CF2-EQUIVALENT</td>
<td>420.33 (242.39)</td>
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Clinical Assessment:
- Positive Symptoms: Positive and Negative Syndrome Scale (PANSS)
- Functional Connectivity: Whole Brain functional connectivity of a priori insula sub-divisions quantified during 7-10 minute resting-state fMRI scan. All results thresholded at whole-brain cluster-level corrected p<.05 for voxel-wise p<.001 (uncorrected).

Insula Sub-Region Seeds Used for Functional Connectivity Analysis

Results

Functional Connectivity of Insula

Dorsal Anterior Insula
- Healthy Controls: Superior Temporal Gyrus
- Schizophrenia: Superior Temporal Gyrus, Dorsal Anterior Cingulate Cortex (dACC)

Ventral Anterior Insula
- Healthy Controls: Bilateral Substantia Innominata, Orbitofrontal Cortex (OFC)
- Schizophrenia: Superior Parietal Lobe

Posterior Insula
- Healthy Controls: Superior Temporal Sulcus
- Schizophrenia: Superior Parietal Cortex, Cerebellum (Ventral Attention Network)

Brain-Behavior Relationships

Dorsal Anterior Insula & Cognitive Ability
- Weaker connectivity between dAI and regions showing hypoconnectivity relative to healthy controls is associated with worse cognition

Ventral Anterior Insula & Negative Symptoms
- Stronger connectivity between vAI and superior temporal sulcus is associated with worse negative symptoms

Conclusions

- All sub-regions of the insula are altered in schizophrenia
- Consistent with a recent report on increased diversity of insula connectivity in schizophrenia\(^6\):
  - PI hyperconnected to regions typically connected to dAI, involved in control of attention
  - dAI hyperconnected to regions typically connected to PI, involved in somatosensory processing
- Hypoconnectivity of dAI→ worse cognitive ability
- Hyperconnectivity of vAI→ superior temporal sulcus→ worse negative symptoms
- Insula connectivity is clearly abnormal in schizophrenia, across all sub-regions, with most widespread alterations in PI. There is some specificity of sub-region connectivity alterations with clinical characteristics, but task-based studies may reveal these relationships more strongly.

References