Jumping to Conclusions and the genetic risk for schizophrenia at First Episode Psychosis

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There are two jars: A mainly red jar containing 60 red and 40 blue beads and a mainly blue jar containing 60 blue and 40 red beads.

Mainly Red Jar
(60 red; 40 blue)

Mainly Blue Jar
(60 blue; 40 red)
The bead drawn is:

Would you like to see any more beads or have you decided now?
The bead drawn is:

Would you like to see any more beads or have you decided now?
Jumping To Conclusions

- Reasoning and data-gathering bias (Garety, 2013).
- Initially studied as a key cognitive component in delusions formation and maintenance (Huq, 1988; Garety, 1999).
- JTC has been found in people at UHR, FEP, patients without delusions and in remission (Broome, 2007; Menon, 2006; Falcone, 2015).

- Associated with proneness to psychotic-like experiences in the general population (Ross, 2015) and with psychotic liability (Van Dael, 2006).
Unresolved points

- No studies to date investigating directly the association with psychosis liability.
- General cognitive ability seems to undermine the association with psychotic disorder.
Aims

to investigate whether IQ plays a role as mediator in the pathway between the bias and the disorder

To test whether JTC is associated with the liability for psychotic disorders through genetic underpinnings of general intelligence.
The EUGEI WP2 case-control study on First Episode Psychosis and population controls

<table>
<thead>
<tr>
<th></th>
<th>Controls N=1293</th>
<th>FEP N=817</th>
<th>Df</th>
<th>Test Statistics</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean; sd)</td>
<td>36.2 (13.1)</td>
<td>30.6 (10.4)</td>
<td>2109</td>
<td>t=10.3</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Gender (male %; N)</td>
<td>47.5 (615)</td>
<td>61.2 (500)</td>
<td>1</td>
<td>Chi²=37.6</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>IQ (mean; sd)</td>
<td>103.6 (17.6)</td>
<td>88.1 (19.2)</td>
<td>1735</td>
<td>t=17.4</td>
<td>p&lt;0.001</td>
</tr>
</tbody>
</table>
Draw-To-Decisions (DTD)
Mediation analysis

• Baron and Kenny’s three-step regression analyses:

<table>
<thead>
<tr>
<th>Step</th>
<th>Analysis</th>
<th>Visual depiction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1</td>
<td>DV regressed on IV (path c)</td>
<td><img src="path_c.png" alt="Diagram" /></td>
</tr>
<tr>
<td>Step 2</td>
<td>MV regressed on IV (path a)</td>
<td><img src="path_a.png" alt="Diagram" /></td>
</tr>
<tr>
<td>Step 3</td>
<td>DV regressed on MV and IV (paths b and c’)</td>
<td><img src="paths_b_and_c_prime.png" alt="Diagram" /></td>
</tr>
</tbody>
</table>

• Sobel-Goodman test to calculate the indirect effect and bootstrap method (5000 repetitions) to test for significance.
Does IQ mediate the association between JTC and psychosis?

Mediation model between case/control status, IQ, and Draws-to-Decision (DTD) Adjusted for age, gender, ethnicity, and country; **p<0.001

Indirect effect= -0.28 (0.21); 95% CI: -0.70 to 0.13; p=0.19
Proportion of total effect mediated=79%

Tripoli et al., 2019, bioRxiv DOI: 10.1101/634352
Polygenic Risk Score for Schizophrenia (SZ PRS) and IQ (IQ PRS)

- SZ PRS and IQ PRS were built using the results from large mega-analyses from Working Groups of the Psychiatric Genomics Consortium (2014) and Savage et al. (2018) respectively.
- Using PRSice, individuals’ numbers of risk alleles in the target sample were weighted by the log odds ratio from the discovery samples, and summed into the PRS at a 0.05 SNPs Pt-threshold.
- We excluded people of homogeneous African ancestry (N=170)
- Total subsample of 519 FEP and 881 controls
Is Jumping to Conclusions directly related to liability for psychosis?

<table>
<thead>
<tr>
<th></th>
<th>B/SE</th>
<th>P value</th>
<th>95% CI</th>
<th>R²</th>
<th>AdjR²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case vs Control(^a)</td>
<td>-0.88/0.25</td>
<td>0.001</td>
<td>-1.38 to -0.38</td>
<td>9%</td>
<td>8%</td>
</tr>
<tr>
<td>SZ PRS(^a)</td>
<td>0.16/0.34</td>
<td>0.64</td>
<td>-0.51 to 0.82</td>
<td>9%</td>
<td>7%</td>
</tr>
<tr>
<td>SZ PRS(^b)</td>
<td>0.47/0.35</td>
<td>0.17</td>
<td>-0.21 to 1.16</td>
<td>9%</td>
<td>8%</td>
</tr>
<tr>
<td>IQ PRS(^a)</td>
<td>0.50/0.13</td>
<td>&lt;0.001</td>
<td>0.25 to 0.75</td>
<td>10%</td>
<td>8%</td>
</tr>
<tr>
<td>IQ PRS(^b)</td>
<td>0.47/0.13</td>
<td>&lt;0.001</td>
<td>0.22 to 0.72</td>
<td>10%</td>
<td>9%</td>
</tr>
</tbody>
</table>

Linear Regressions of Polygenic Risk Scores Predicting DTD; \(^a\)Adjusted for age, gender, and 20 principal components for population stratification; \(^b\)Adjusted for case/control, age, gender, and 20 principal components for population stratification

Tripoli et al., 2019, bioRxiv DOI: 10.1101/634352
Conclusions

• IQ accounts for about 80% of the effect of psychosis on JTC. That is, case/control differences in JTC were not only partially mediated but were fully mediated by IQ.

• The occurrence of jumping to conclusions cannot be explained by SCZ PRS

• The IQ PRS added significant variance explained to the predicting model

• The genetic association between JTC and psychosis is potentially mediated by the underlying genetic basis of IQ, rather than being influenced by the genetics of psychosis directly.
Acknowledgements

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THANK YOU FOR YOUR ATTENTION

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