Neuroimaging of Psychotic Disorders

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Overview

NEUROIMAGING
• Pneumoencephalography
• CT
• sMRI*
• DTI / DWI
• MRS
• SPET and PET*
• fMRI
• EEG, MEG

PSYCHOTIC DISORDERS
• Schizophrenia*
• Schizo-affective disorder
• Bipolar (psychotic symptoms)
• Depression (psychotic symptoms)
• Delusional disorder
• Acute & transient / Brief psychotic disorder
Computerised Tomography

Johnstone et al, Lancet 1976

Lewis BJPsych 1990: Most consistent correlate of increased VBR is: Cognitive impairment (in 11/14 studies)

Cf DTI studies
Magnetic Resonance Imaging


- compatible results with region of interest and automated voxel-based approaches (Honea et al, Am J Psych 2005; 162:2233-45)

- WBV reduction corroborated by post-mortem studies (2% weight reduction, Harrison et al, Schizo Res 2003)

- reduced superior temporal gyrus size repeatedly correlated with positive symptom severity - especially of hallucinations (18/35 studies found correlations AVHs/Th.Dis. in Sun, Brain Res Rev 2009; Palaniyappan et al, Schizo Res, 2012; Modinos et al, Cortex 2013)
Prefrontal (OFC) cortical thinning links to negative symptoms in schizophrenia (ENIGMA consortium; Psychol Med 2017)

&

Cortical and subcortical size in Pts & Rels
(1,228 FDRs-SZ, 852 FDRs-BD, 2,246 Cons, 1,016 Pts Sz, 666 Pts BPD)
100K+ subjects in total, 4 continents, 35 countries, 302 co-authors

108 GWS loci, including Dopamine D2 receptor, Glutamate (6), Neuronal Ca Signalling & Channels (N=7 incl. CACNA1C on Chr.12), other ion channels (Potassium, Nicotinic CHRNA3/A5/B4 on Chr.15)

These polygenic effects are additive, can be calculated individually and account for up to 20% of liability to develop schizophrenia (and other disorders)
PGRS-SCZ negatively associated with cortical thickness and volume in UKB (N=2,864)
(Neilson et al, Biol Psychiatry in press)

Beta = -0.043, \( p = 0.012 \)
Variance explained = 0.2%

Beta = -0.033, \( p = 0.039 \)
Variance explained = 0.1%
Environmental influences on neurodevelopment pre-schizophrenia – childhood adversity & drugs


Longitudinal volume reductions in people at high genetic risk of schizophrenia as they develop psychosis.

Analysis of all 434 scans in EHRS
Analysis by mixed model ANOVA

Strong correlations with increasing positive psychotic symptoms

e.g. % yearly reduction in PFL correlates:
  r ~.6 with increasing Hallucinations,
  r ~.4 with increasing Passivity &
  r ~.5 with increasing Delusions
Twenty-seven studies included, with 928 patients and 867 control subjects, and 32 different regions of interest.

Subjects with schizophrenia showed significantly greater decreases over time in:
- whole brain volume & gray matter,
- frontal gray and white matter,
- parietal white matter, and
- temporal white matter volume,
as well as larger increases in LV volume.

The differences between patients and control subjects in annualized percentage volume change were:
- .07% for whole brain volume,
- .59% for whole brain gray matter,
- .32% for frontal white matter,
- .32% for parietal white matter,
- .39% for temporal white matter, and
+ .36% for bilateral lateral ventricles.

Causes:
Risk Genes
Alcohol
Drugs
Inactivity

Effects:
Poor outcome (5/5 refs)

?Remediable
Antipsychotics and GMV

Fig. 2. Meta-regression analysis:
(a) progressive GMV changes and cumulative exposure to antipsychotics ($\beta = -0.013$, CI 95% from $-0.033$ to $-0.001$, $p = 0.048$);
(b) progressive GMV changes and duration of illness (DOI, $\beta = 0.001$, CI 95% from $-0.001$ to $0.001$, $p = 0.653$);
(c) progressive GMV changes and psychotic symptoms change over follow-up time ($\beta = 0.002$, CI 95% from $-0.011$ to $0.016$, $p = 0.732$).

The size of the circle reflects the sample size of the study. Negative values on the y axis indicate brain volume reductions at follow-up as compared to baseline. Cumulative exposure to antipsychotics unit was defined in Chlorpromazine Equivalent per day (CPZ-EQ/d) multiplied by the duration of the medication treatment in days.

Fusar-Poli et al, NSBBR 2013
### Diagnostic prediction of transition to psychosis

**Multi-class performance**

<table>
<thead>
<tr>
<th></th>
<th>HC (n=17)</th>
<th>Transition (n=15)</th>
<th>Non-Transition (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity [%]</td>
<td>82</td>
<td>87</td>
<td>76</td>
</tr>
<tr>
<td>Specificity [%]</td>
<td>94</td>
<td>89</td>
<td>91</td>
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<tr>
<td>Accuracy [%]</td>
<td>90</td>
<td>88</td>
<td>86</td>
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</tbody>
</table>

Discriminative pattern of classification “Transition vs Non-Transition”

GM volume decrements

GM volume increments

Koutsouleris et al. 2009, Archives General Psychiatry
Predicting schizophrenia with MRI
SVM Results from EHRS 2.5yrs pre-onset

- Diagnostic performance was examined using:
  - structural MRI data alone
  - in combination with both clinical variables

Table: Diagnostic performance of the SVM-RFE method in 17 HR+ versus 17 HRill.

<table>
<thead>
<tr>
<th></th>
<th>only sMRI analysis</th>
<th>Combined sMRI-clinical analysis</th>
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<tr>
<td>Features selected</td>
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Zarogianni et al, Schizo Research 2017 & 2018
Conclusions

• General trend evident for larger studies using complimentary methods across centres
• Schizophrenia clearly associated with several disruptions in brain structure and chemistry
• These are due to multifactorial pre-morbid, peri-onset and post-diagnostic factors
• Clinically relevant uses of brain imaging (for early diagnosis) is possible & currently being evaluated in several large EU and US studies - but multivariate, N-of-1, therapeutic and ethical questions remain