Early motor, cognitive, and neural predictors of schizophrenia spectrum disorders (SSDs)

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Motor Abnormalities

• In SSD we see:
  • 50-65% with neurological soft signs (Heinrichs & Buchanan, 1988)

• Predictors
  • Neurological soft signs in infancy:
    • Odds ratio (OR) of 4.6; specific to SSDs (Cannon et al., 2002; Schiffman et al., 2009)
  • Unusual movements/postural abnormalities in infancy: ORs of 2-5 (Rosso et al., 2000)
  • Neurological soft signs and motor coordination and in middle childhood:
    • ORs up to 20 (Cannon et al., 2002);
    • Motor coordination specific to SSDs (Cannon et al., 2002; Leask et al., 2002)
• Up to 80% of individuals with SSDs experience cognitive impairment (Reichenberg et al., 2009; Keefe et al., unpublished)

• Middle Childhood Predictors
  • Worse processing speed than siblings (Niendam et al., 2003), medium ES
  • Worse working memory than siblings (Niendam et al., 2003) and than high risk individuals who do not develop SSDs (Cornblatt et al., 1999), medium ES
  • Working memory predicts development of SSDs in high risk offspring (sensitivity 83%, specificity 72%) (Erlenmeyer-Kimling et al., 2001)

• Adolescent Predictors
  • Worse school test score than predicted by family education (Kenlder et al., 2016), with hazard ratios up to 3.6

Cognitive Function

Keefe et al., unpublished data from NeuroCog Trials with Schizophrenia Spectrum Disorders (Ns = 4843 to 4992)

% with T-Scores below 40

Processing Speed  Attention  Working Memory  Verbal Learning  Visual Learning  Reasoning and Problem Solving  Composite Score

standard
Intelligence (IQ)

• 61% of individuals with SSD have “premorbid” IQs in the below average range (Keefe et al., unpublished)

• Low IQ in middle childhood strongly predicts the likelihood of developing schizophrenia in cohort-based and case-control studies
  • For each standard deviation increase in IQ, 42% reduction in lifetime odds of SSD (Koenen et al., 2009)
  • OR of 7.89 of having schizophrenia if IQ < 70
  • Prediction stronger if you also have genetic risk (Kendler et al., 2015)
  • But … predicts reduced odds of many other disorders (Koenen et al., 2009; Osler et al., 2007; Sorenson et al., 2010)
Neural Impairments

• Individuals with SSDs show:
  • Meta-analyses show reduced volumes/thickness of thalamus, hippocampus, and insula, anterior cingulate, and prefrontal cortex (e.g., Haijma et al., 2013)
  • Meta-analyses show reduced dorsolateral prefrontal cortex activation in executive function and working memory tasks (Minzenberg et al., 2009)
  • Reduced thalamic to prefrontal and cerebellar connectivity, but increased thalamic to sensory motor areas (Review, Giraldo-Chica & Woodward, 2016)
Neural Impairments

- **Family High Risk Studies**
  - Reduction in *inferior frontal gyrus* volume over time, 38% sensitivity, 96% specificity (Job et al., 2006)

- **Clinical high risk who developed SSDs:**
  - Meta analysis → lower gray matter volume in *insula, anterior cingulate, prefrontal cortex* and *cerebellum* (Smieskova et al., 2010), with varying effect sizes across regions
    - But NAPLS did not see volume or thickness differences at baseline between converters and non-converters (Cannon et al., 2014)
  - Greater *prefrontal* volume loss over time to conversion (Sun et al., 2009; Cannon et al., 2014)
  - Reduced *thalamic* to *prefrontal* and *cerebellar* connectivity, but increased thalamic to sensory motor areas (Anticevic et al., 20016)
Next Steps

• Birth cohort and case-control studies that:
  • Assess range of cognitive domains, rather than only 1 or 2
  • Assess specificity to SSDs
  • Assess increased predictive utility when combined with other potential predictors
  • Assess neural predictors in children, ideally even in infants
  • Adolescent Brain and Cognitive Development (ABCD) Study will provide very relevant data