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21.4 BASELINE CLINICAL AND BIOLOGICAL VARIABLES PREDICTING 1 YEAR OUTCOME OF SUBJECTS AT CLINICAL HIGH RISK OF PSYCHOSIS: INSIGHT FROM SHANGHAI AT RISK FOR PSYCHOSIS (SHARP) PROGRAM

Citation
Zhang, T., H. Li, Y. Tang, C. Li, K. Woodberry, D. I. Shapiro, M. Niznikiewicz, et al. 2018. "21.4 BASELINE CLINICAL AND BIOLOGICAL VARIABLES PREDICTING 1 YEAR OUTCOME OF SUBJECTS AT CLINICAL HIGH RISK OF PSYCHOSIS: INSIGHT FROM SHANGHAI AT RISK FOR PSYCHOSIS (SHARP) PROGRAM." Schizophrenia Bulletin 44 (Suppl 1): S36. doi:10.1093/schbul/sby014.088. http://dx.doi.org/10.1093/schbul/sby014.088.

Published Version
doi:10.1093/schbul/sby014.088

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in part on Larry's seminal work, many in the field have come to view schizophrenia as fundamentally a disorder of dysconnection within and between certain functional networks in the brain. However, what levels or patterns of dysconnection may be sufficient for overt psychosis remains unclear. Because schizophrenia is complexly determined, clinically heterogeneous, and (frequently) chronic and debilitating, neuroimaging studies comparing those with and without this condition cannot by themselves differentiate which neural changes contribute causally, which are epiphenomena, and which are secondary to factors associated with chronicity of illness or antipsychotic drug treatment. A crucial aim is thus isolation of the changes immediately preceding the onset of psychosis that, by virtue of their temporal priority, may represent primary mechanisms in the cascades of events leading to the emergence of psychosis.

Methods: Identifying such changes requires a paradigm for ascertaining at-risk individuals prior to psychosis onset and following them over time. Larry Seidman's early work found that both patients and their first-degree relatives fail to disengage the default mode network and fail to engage task-positive networks under cognitive challenge. In the early 2000's, in an effort to isolate changes in brain structure and function more proximal to the onset of psychosis, Larry joined with seven other investigators to launch the North American Prodrome Longitudinal Study (NAPLS). This talk will focus specifically on neuroimaging markers and on results examining baseline and longitudinal changes in brain structure and function among clinical high-risk (CHR) and control subjects, who were scanned at baseline and at 12-months or the point of conversion if it occurred earlier.

Results: Converters to psychosis showed a significantly steeper rate of gray matter thinning in right superior and medial prefrontal cortex (PFC) and greater ventricular expansion than non-converters and controls. These effects were significant controlling for multiple testing and independent of exposure to antipsychotic drugs. Higher levels of proinflammatory cytokines at baseline were predictive of steeper rates of gray matter reduction in superior and medial PFC, consistent with the notion that progressive gray matter change in this context is likely to reflect dendritic retraction and synaptic pruning driven by microglial activation. This interpretation is further supported by recent evidence of genetic susceptibility mechanisms involving complement signaling in schizophrenia, variations that appear to result in over-pruning of cortical synapses in animal models. In smaller subsamples using both task-based and resting-state fMRI, CHR subjects who converted to psychosis showed a progressive decrease in global efficiency and increase in network diversity from baseline to follow-up at the point of conversion. The identified network alterations were highly correlated with each other and with progressive gray matter changes in the prefrontal cortex in converters.

Discussion: These results are suggestive of a progressive loss of gray matter potentially triggered by altered immune signaling leading to over-pruning of synapses and provide preliminary evidence for longitudinal reconfiguration of resting-state and task-positive brain networks during psychosis development. The latter results appear to converge with Dr Seidman's pioneering work on default mode and task-positive network function in individuals at genetic risk for schizophrenia.

21.4 BASELINE CLINICAL AND BIOLOGICAL VARIABLES PREDICTING 1 YEAR OUTCOME OF SUBJECTS AT CLINICAL HIGH RISK OF PSYCHOSIS: INSIGHT FROM SHANGHAI AT RISK FOR PSYCHOSIS (SHARP) PROGRAM

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Background: In 2010, the "ShangHai At Risk for Psychosis (SHARP)" study was launched at the Shanghai Mental Health Center (SMHC), the largest outpatient mental health clinic in China. The Chinese SHARP research was led by Dr. Larry Seidman, who was also the PI of the Harvard site of the NAPLS project. He had implemented methods very similar to those used in NAPLS for the identification of clinical high risk (CHR) individuals in Mainland China in studies jointly funded by the United States National Institute of Mental Health and Chinese funding agencies.

Methods: Dr. Seidman began a collaboration with the SMHC by advising us in carrying out an epidemiological study and then received joint funding for an R21 MH093294 (Fogarty/NIH, "Broadening the Investigation of Psychosis Prodrome to Different Cultural Groups") designed to implement a variety of clinical, neurocognitive and event related potential (ERP) measures in a preliminary study of CHR. That study, which began in April 2012 and ended in March 2015, aimed to build research capacity at the SMHC. He guide us provided 4 in-person research and clinical skills trainings (2 in SMHC, 2 in Boston), translated a widely used CHR diagnostic instrument (the Structured Interview for Prodromal Symptoms/SIPS), and trained China partners to conduct a preliminary study of 100 CHR individuals. Building upon the R21 project, and the North American Prodrome Longitudinal Studies (NAPLS) model, the same group of researchers led by Dr. Seidman is collaborating on an NIMH R01 101052-01 project (2013 to 2016) to examine biomarkers of CHR with 1 year follow-up. The R21 and R01 collaborations between Harvard Medical School (HMS), MIT, Florida A&M University (FAMU), and SMHC investigators have capitalized on the resources and experiences of the Harvard researchers as members of NAPLS, MIT researchers' leading role in functional magnetic resonance imaging (fMRI), and FAMU researchers' expertise in bridging western and Chinese cultures to enhance the existing capacity of Chinese researchers studying the biopsychosocial aspects of CHR. Finally, a stratified cohort of 300 CHR participants was recruited between 2012–2015, and followed up for at least 1 year.

Results: With the hope of Dr. Seidman, the SHARP project is ongoing and getting better, larger and stronger. Of the total 417 CHR participants (previous epidemiological survey [CHR, n = 117], R21 [CHR, n = 100], R01 [CHR, n =200]), 349 completed at least a year of follow-up (until August 30, 2017; the longest follow-up case was six and a half years), in which 83 converted to psychosis, and 68 were lost. Preliminary data showed about 20% CHR converted to a psychotic disorder over the course of follow-up, several clinical factors such as 1) functional decline; 2) selected positive symptoms(unusual thoughts and suspiciousness); 3) selected negative symptoms(social anhedonia, expression of emotion, and ideational richness); biological factors such as the P300 auditory ERP; fMRI: Reduced anti-correlation between the bilateral parietal lobule and left dorsolateral prefrontal cortex; Structural MRI: superior temporal gyrus. et al. are account for increasing the risk of conversion to full psychosis.

Discussion: This is the first, well-implemented, longitudinal study of CHR in a low and middle-income country to comprehensively investigate clinical and biological factors in predicting psychosis conversion and illness progression. Dr. Seidman provide a critical step in the implementation of CHR concept in China, just as an obvious need and urgency for prevention and early intervention for Chinese patients with schizophrenia.