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Disrupted latent inhibition in individuals at ultra high-risk for developing psychosis

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ABSTRACT

The addition of off-the-shelf cognitive measures to established prodromal criteria has resulted in limited improvement in the prediction of conversion to psychosis. Tests that assess cognitive processes central to schizophrenia might better identify those at highest risk. The latent inhibition paradigm assesses a subject's tendency to ignore irrelevant stimuli, a process integral to healthy perceptual and cognitive function that has been hypothesized to be a key deficit underlying the development of schizophrenia. In this study, 142 young people at ultra high-risk for developing psychosis and 105 controls were tested on a within-subject latent inhibition paradigm. Additionally, we later inquired about the strategy that each subject employed to complete the test, and further investigated the relationship between reported strategy and the extent of latent inhibition exhibited. Unlike controls, ultra high-risk subjects did not demonstrate a significant latent inhibition effect. This difference between groups became greater when controlling for strategy. The lack of latent inhibition effect in our ultra high-risk sample suggests that individuals at ultra high-risk for psychosis are impaired in their allocation of attentional resources based on past predictive value of repeated stimuli. This fundamental deficit in the allocation of attention may contribute to the broader array of cognitive impairments and clinical symptoms displayed by individuals at ultra high-risk for psychosis.
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1. Introduction

Efforts to establish criteria that identify individuals at highest risk for schizophrenia have had limited success (Yung et al., 2005; Cannon et al., 2008; McGorry et al., 2008). Recent work has attempted to improve predictive capability by supplementing current prodromal symptom criteria with neurocognitive measures (Brewer et al., 2005, 2006; Keefe et al., 2006). However, many of the cognitive assessments explored to date have used off-the-shelf tests designed for measuring intelligence or brain damage. Methodologies that probe specific cognitive impairments characteristic of the at-risk state may yield greater risk prediction specificity.

Recent theories of brain function have suggested that a central role of the human brain is to encode hierarchical memories that emphasize the commonality of experiences across time and to use these "invariant" memories to continually predict the next moment of experience, a process we have termed learning-dependent predictive perception (LDPP) (Hawkins and Blakeslee, 2004; Krishnan et al., 2011b). LDPP employs regularities in past experience to guide the allocation of attentional and cognitive resources, thus facilitating efficient and appropriate interaction with the world. In fact, it has been postulated that the columnar circuitry present throughout the neocortex aids these processes (Hawkins and Blakeslee, 2004) and thus LDPP is a fundamental function of neocortical architecture. We have hypothesized that individuals with schizophrenia exhibit impaired LDPP function and that deficits in LDPP may be a key cognitive risk factor for developing psychosis (Keefe et al., 2011; Kraus et al., 2009; Krishnan et al., 2011a, 2009). As such, we believe that cognitive

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tests that assess aspects of LDPP may be especially sensitive predictors of conversion to psychosis (Keefe and Kraus, 2009).

We have been testing the hypothesis that LDPP is impaired in individuals at high risk for developing schizophrenia. The Longitudinal Youth at Risk Study (LYRIKS) is a prospective, observational, single-site project conducted in Singapore to identify the clinical, cognitive and biological factors that predict the development of psychosis (Chong et al., 2011). The study identified youth at ultra high-risk (UHR+) for developing psychosis and then followed these individuals for 2 years, assessing their neurocognitive function at 6 month intervals [For a complete description of the neuropsychological battery, see Lee et al. (2013)].

Here we report the results from one test of LDPP function, the Latent Inhibition (LI) test. Pre-exposure to a conditioned stimulus in the absence of an unconditioned stimulus inhibits conditioning when the stimuli are subsequently paired, a phenomenon termed *latent inhibition*. This paradigm tests the viability of the LDPP system by assessing a participant's tendency to ignore stimuli that had been irrelevant to task performance previously and focus on stimuli that are more likely to aid task performance. This ability to filter out irrelevant stimuli and focus on meaningful stimuli is crucial to the efficient allocation of perceptual and cognitive resources and impairment in this ability has been hypothesized to underlie the development of psychosis (Gray et al., 1991; Kapur, 2003). Reduced LI has been demonstrated in unmedicated and/or acute schizophrenia patients (Baruch et al., 1988a) and LI scores have exhibited strong correlations with schizotypal traits and degree of latent inhibition in the general population (Baruch et al., 1988b). In this study, we have for the first time assessed the latent inhibition effect in a group of young people at high-risk for developing psychosis.

2. Method

2.1. Overall study design

The design of the overall study is described in detail elsewhere (Lee et al., 2013). The study was approved by the National Healthcare Group's Domain Specific Review Board and all study procedures were carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. Recruitment adopted a hybrid approach that has been described in greater detail in an earlier publication (Mitter et al., 2014). Both help-seeking and non-help-seeking individuals in the community were approached for this study. The inclusion criteria for the study were (i) youths between 14 and 29 years old and (ii) English-speaking because of the neurocognitive measures. Participants were excluded if they (i) had a past or current history of psychosis or mental retardation, (ii) were currently using illicit substances, (iii) were taking antipsychotics or mood stabilizers, or (iv) had medical causes associated with their psychosis.

The CAARMS (Yung et al., 2005) positive symptoms subscale was used to determine the risk status of each participant. The CAARMS was administered by either psychiatrists or research psychologists. The administrators attended a 1-week intensive training at the Personal Assessment and Crisis Evaluation Clinic (PACE), in Melbourne, Australia. Inter-rater reliability was established at >0.9. Supervision was provided by two on-site research clinicians and at monthly rater meetings. The CAARMS composite score was computed, by weighting intensity (I) of symptoms by their frequency (F) within the four domains of the CAARMS Positive Scale — Unusual Thought Content (UTC), Non-Bizarre Ideas (NBI), Perceptual Abnormalities (PA) and Disorganized Speech (DS), according to the formula $(Iutc * Futc) + (Inbi * Fnbi) + (Ipa * Fpa) + (Ids * Fds)$.

The LI task was included as part of the neurocognitive battery, consisting of standard neuropsychological tests, as well as experimental tests included to assess specific aspects of LDPP. Due to technical issues, the latent inhibition test was not ready at the start of the study, resulting in a large amount of missing data that prohibits its inclusion in the longitudinal analyses involving the rest of the neurocognitive battery, which will be reported elsewhere.

2.2. Latent inhibition test design

The LI task was programmed in MATLAB version 7.8.0.347 (R2009a), based on the design of Schmidt-Hansen et al. (2009) and the task was run on a 17 inch Dell laptop.

When the task was started, the screen displayed the instruction "Look for X". Participants were then read the following instructions (as used by Schmidt-Hansen et al. (2009)): *This is a reaction time test which lasts for about 7 minutes. In this task I want you to watch the sequence of letters. Your task is to try to predict when the letter "X" is going to appear. If you think that you know when the "X" will appear, then you can press the spacebar early in the sequence. Alternatively, press as quickly as you can when you see the "X". There may be more than one rule that predicts the "X". Please try to be as accurate as you can, but do not worry about the occasional error.*

The LI test consisted of two phases, a pre-exposure phase and a test phase divided into two blocks. In the pre-exposure phase, the pre-exposed (PE) letter was presented 10 times, intermixed with 4 different filler letters, each presented a total of 14 times in a fixed pseudo-random sequence. The sequence was constrained by the rule that no stimulus should be presented in consecutive presentations. The test phase immediately followed the pre-exposure phase with no break in between.

In each test block, the target stimulus (the letter X) was presented 24 times. Filler letters were interspersed with the presentation of the target. Each filler letter was presented an average of 27 times per block, with the target letter immediately following on 2 of the trials (7.4% of trials) for each filler letter per block. During the test phase, a non pre-exposed (NPE) letter (a letter that was not presented during the pre-exposure phase) and the PE letter were presented 8 times per block and were always followed by the presentation of the target (100% of trials). Each letter was black, 1.2 cm high and presented on a white background for 1000 ms with no inter-stimulus interval. The rationale behind this method is that subjects will learn during the pre-exposure phase that pre-exposed letters do not precede the target letter, thus their reaction time to targets that are preceded by pre-exposed letters will be longer than targets preceded by non-pre-exposed letters. The key comparison for the test is the number of anticipatory responses and mean reaction time to targets following an NPE predictor compared to a PE predictor (Schmidt-Hansen et al., 2009). The presentation order of all stimuli was fixed across all participants. Also, the presentation order was fixed across assessments, but filler, PE and NPE letters were rotated across versions of the test. X was always used as a target and all consonants except K and Y (which were deemed to be too visually similar to X) were rotated such that none appeared in more than 2 non-consecutive versions and no letter was used as a PE or NPE on more than 1 version. The task lasted approximately 7 min.

Because early testing indicated a large range of reaction times for the PE and NPE trials in both UHR− and UHR+ subjects, we questioned whether these differences were due to different strategies employed to perform the task. Thus, we began explicitly asking subjects about the strategy they used. Immediately following completion of the test, the psychometrician asked the following two questions: 1) "What was your strategy for doing that task?" and 2) "Was there anything you did to try to respond more quickly when the X came up?" Participants' responses were then classified into one of five categories: 1) Optimal (participants mentioned that both the PE and NPE stimuli reliably predicted X, 2) Favoring the PE stimulus (participants specifically mentioned only that the PE stimulus

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