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The cerebellum and learning of non-motor associations in individuals at clinical-high risk for psychosis

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ABSTRACT

The cerebello-thalamo-cortical circuit (CTCC) has been implicated in schizophrenia. However, this work has been limited to structural and functional networks, or behavior, and to date, has not been evaluated in clinical high-risk (CHR) youth, a group at elevated risk for psychosis. Here, we used an innovative learning paradigm known to activate the CTCC (while limiting potential motor confounds) to evaluate CHR and healthy control individuals during functional magnetic resonance imaging (fMRI). 20 CHR and 21 healthy control individuals performed a second-order rule learning task while undergoing fMRI. This was preceded and followed by the paradigm under dual-task conditions. In addition, all participants underwent structured clinical interviews to confirm a prodromal syndrome and assess symptom severity. The rate of learning did not differ between groups. However, the CHR group consistently performed more poorly under dual-task conditions, and exhibited a higher dual-task cost after learning. Further, learning rate in the CHR group was significantly associated with symptom severity. Both groups showed activation in regions of the CTCC. During early learning, the CHR group exhibited greater engagement of regions of the default mode network, suggesting that they were less able to engage the appropriate task positive networks. During late learning, there were qualitative differences wherein controls showed more prefrontal cortical activation. Higher order cognitive rule learning is related to symptom severity in CHR individuals. fMRI revealed that CHR individuals may not reliably disengage the default mode network, and during late learning high-risk youth may not engage the prefrontal cortex as extensively as controls.

1. Introduction

Understanding the pathophysiology of schizophrenia is critical for the development of effective interventions, and for prevention prior to disease onset. One of the leading frameworks for conceptualizing the wide range of symptoms and the cognitive impairments associated with schizophrenia is that of cognitive dysmetria (Andreasen et al., 1996, 1998). This theory holds that schizophrenia is associated with uncoordinated thoughts that result in the disparate symptoms and cognitive difficulties seen in these patients. Seminal work outlining this theory implicated cerebellar and prefrontal brain regions (Andreasen et al., 1996), suggesting that the cerebello-thalamo-cortical circuit (CTCC) may play a key role in cognitive dysmetria. The cerebellum has been suggested to play a critical role in the coordination of fluid motor behaviors (Imamizu et al., 2000; Ito, 2008; Ramnani, 2006), though cerebellar circuitry (Bernard et al., 2012; Dum and Strick, 2003; Kelly and Strick, 2003; Salmi et al., 2010) allows for a parallel role in the coordination of thought (Ito, 2008; Ramnani, 2006). Dysfunction in the CTCC network may therefore contribute to cognitive dysfunction, as well as symptom severity, particularly disorganized symptoms, as seen in patients with schizophrenia (Andreasen et al., 1996).

In more recent years, work investigating the CTCC and cerebellum in patients with schizophrenia has revealed that cerebellar dysfunction is present in this population (Andreasen et al., 1996, 1998; Andreasen and Pierson, 2008; Bernard et al., 2017a, 2017b; Bernard and Mittal, 2015; Kim et al., 2014; Shergill et al., 2005). Moreover, our recent work

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demonstrates CTCC dysfunction prior to the onset of psychosis during the clinical high risk (CHR) period (Bernard et al., 2014; Bernard et al., 2017a, 2017b; Dean et al., 2013, 2015; Mittal et al., 2014). Notably, this work demonstrates CTCC dysfunction in a population that is not impacted by many of the confounds seen in patients with schizophrenia. Further, we recently found that the integrity of CTCC functional circuits was predictive of symptom progression over time (Bernard et al., 2017a, 2017b). Together, this suggests that CTCC dysfunction may be related to the pathophysiology of psychosis, and that dysfunction in this circuit may contribute to disease progression.

With that said, the existing perspective of CTCC dysfunction in CHR populations is limited in several key ways. First, the majority of our work to date has focused on structure and resting state networks (Bernard et al., 2014; Bernard et al., 2017a, 2017b; Dean et al., 2013; Mittal et al., 2013). Evidence for differences in functional activation of the cerebellum and prefrontal cortex, paralleling what was found by Andreasen and colleagues in patients with schizophrenia (Andreasen et al., 1996) is lacking. Support for altered functional engagement prior to the onset of formal psychosis would provide key evidence suggesting that CTCC dysfunction is part of the pathophysiology of psychosis. Second, we have been largely focused on motor behaviors (Bernard et al., 2014; Dean et al., 2013, 2015; Mittal et al., 2014), while the cognitive dysmetria theory has been framed in terms of non-motor behavior.

In our recent work, we suggested that dysfunctional internal models and deficits in internal model formation may result in dysmetria of thought in schizophrenia (Bernard and Mittal, 2015). While motor learning has been the primary domain of investigation for the study of internal model formation (Imamizu et al., 2000), Balsters et al. (2013) recently developed a rule-learning task that dissociated motor responses from the cognitive (second-order) rule that was learned. With their experimental design and scanning parameters they were able to separately investigate the activation associated with the second-order rule from the processing and activation associated with executing a motor response. They demonstrated activation in the lateral posterior regions of the cerebellum (Crus I and Crus II) during the learning of non-motor rules (Balsters et al., 2013). This task allows us to investigate learning and internal model formation in the non-motor domain. In doing so, we can test the idea that cognitive dysmetria and dysfunctional internal model formation are present in CHR populations prior to the onset of formal psychosis. If such deficits are present, this would then suggest that cerebellar dysfunction, specifically the formation of internal models, is present prior to the onset of formal psychosis in at-risk individuals, and may be related to the pathophysiology of psychosis. In what is, to our knowledge, the first fMRI study of cerebellar function in CHR youth, we used the task developed by Balsters et al. (2013) to investigate non-motor learning. First, we expected lateral posterior cerebellar activation during the learning of new cognitive rules, consistent with Balsters et al. (2013). Second, we expected to see group activation differences, wherein activation would be decreased in the CHR group. Behaviorally, we expected to see performance deficits in the CHR group, particularly under dual-task conditions after learning, consistent with the extant literature demonstrating cognitive deficits in CHR populations (Bora and Murray, 2013) and in psychosis. Finally, we hypothesized that if internal model formation and cognitive dysmetria were related to disease, we would see correlations with symptom severity, particularly in disorganized and positive symptoms (Andreasen et al., 1996, 1998).

2. Methods

2.1. Participants

Here, we investigated 20 adolescent and young adult CHR individuals (mean age = 20.8 ± 1.54 years, 7 female), and 21 healthy controls (mean age = 21.5 ± 1.83 years, 11 female). See Table 1 for demographic information. All participants had previously enrolled in a longitudinal study investigating psychosis risk as part of the Adolescent Development and Preventative Treatment (ADAPT) research program at the University of Colorado Boulder. Participants were recruited for participation in this investigation at the end of their annual study visit, or were directly contacted over the phone. Prior to beginning the study all participants signed an IRB-approved consent form. Exclusion criteria for both groups included a history of head injury, the presence of a neurological disorder, life-time substance dependence as assessed by the Structured Clinical Interview for Axis-I DSM IV Disorders (First et al., 1995), and the presence of any contraindications for the magnetic resonance imaging environment. In the CHR group, we also excluded individuals with an Axis I psychotic disorder. In the control sample, we excluded individuals with any diagnosis of an Axis I disorder. Further, the presence of a psychotic disorder in first-degree relatives was an additional exclusion criterion for the control group.

Table 1
Participant demographics and symptom severity. Mean (± standard deviation). Significant group differences are also indicated.

		CHR	Control
N		20 (7 female)	21 (11 female)
Age (years)		20.8 (1.54)	21.5 (1.83)
Parent education (years)		16.55 (1.82)	15.90 (2.96)
Participant education (years)		13.55 (1.32)	14.28 (1.48)
Alcohol use		1.7 (0.47)	1.81 (0.40)
Marijuana use		1.5 (0.51)	1.38 (0.49)
Symptom severity	Positive***	12.1 (4.39)	0.38 (0.86)
	Negative***	13.5 (8.35)	0.52 (0.75)
	Disorganized***	6.65 (3.57)	0.24 (0.54)
	General***	8.15 (3.85)	0.38 (0.74)

*** $p < 0.001$.

2.2. Symptom assessment

The Structured Interview for Prodromal Syndromes (SIPS) measures distinct categories of prodromal symptom domains (positive, negative, disorganized, general) and is scored from 0 to 6 for each symptom. Inclusion in the CHR group was determined by moderate levels of positive symptoms (a SIPS score of 3–5 in one or more of the 5 positive symptom categories), and/or a decline in global functioning in association with the presence of schizotypal personality disorder, and/or a family history of schizophrenia (Miller et al., 1999). All interviewers had inter-rater reliabilities that exceeded Kappa ≥80. Because we were recruiting participants from an ongoing study, if the individual had been administered the SIPS (and SCID-IV) within one month prior to the scan, those assessments were used to minimize participant burden. For those with assessments over one month from the time of scan, individuals underwent an additional clinical interview. The frequency of alcohol and marijuana consumption was measured based on self-report on a scale from 0 to 5 where 0 indicates “never uses” and 5 indicates “daily use” (Drake et al., 1996).

2.3. Second-order rule learning task

In order to assess non-motor rule learning while targeting the CTCC, we used a second-order rule learning task developed by Balsters et al. (2013). This task was designed to dissociate the motoric response to a visual stimulus from the rule-learning itself. To do so, we used an event-related imaging design (described in more detail below) wherein we were able to dissociate the activation associated with the rule itself, from that associated with the preparation and execution of the motor response. Because we were particularly interested in cerebellar activation during learning in a non-motor paradigm in CHR individuals, we adapted the second-order rule learning condition to investigate group differences in cerebellar activation during learning. In order to focus on