Postural Control and Verbal and Visual Working Memory Correlates in Nonclinical Psychosis

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Keywords

Nonclinical psychosis · Postural control · Cerebellar-thalamic-cortical-cerebellar circuit · Working memory

Abstract

Introduction: Motor and cognitive abnormalities are well documented in psychosis spectrum disorders. Evidence suggests these deficits could be pronounced because of disruptions in the cerebellar-thalamic-cortical-cerebellar (CTCC) circuit, a network thought to be heavily implicated in motor and higher cognitive functioning. Although significant research has been done on this topic in individuals with schizophrenia and those at a clinical high risk for psychosis, much less is known about deficits at the lower end of the spectrum.

Methods: In this study, we extended the understanding of motor abnormalities across the psychosis continuum by examining postural sway deficits in the nonclinical psychosis (NCP) population. Furthermore, we linked these deficits to verbal and visual working memory. High-NCP ($n = 37$) and low-NCP control ($n = 31$) participants completed an instrumental balance task, highly sensitive to subtle variations in postural sway, along with a brief working memory battery.

Results: We found that high-NCP participants presented with increased postural sway area (i.e., worse postural con-

trol) relative to low-NCP controls on a difficult condition (with limited proprioceptive cues), but not on an easier condition. Furthermore, results indicated that the sway area was correlated with poorer performance on working memory tasks in the high-NCP group. **Conclusion:** These findings suggest that CTCC circuit abnormalities are present across the lower end of the psychosis spectrum and that they may be contributing to a range of motor and cognitive behaviors seen in the population. However, evidence suggests that the signs are subtle, and that sensitive assessment devices and challenging conditions may be necessary for detection.

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Introduction

An accumulating body of research suggests that psychotic experiences exist on a phenotypic continuum, from disorders such as schizophrenia at the severe end to subclinical levels of fleeting psychotic-like experiences at the lower end [1–3]. With respect to the latter group, in recent years we have come to understand that a sizable subset of the general population (5–13%; [1, 2, 4]) reports nonclinical psychosis (NCP) symptoms. While these symptoms include experiences that characterize formal

psychosis (e.g., unusual thoughts or hallucinations), they are brief, rare, and are not accompanied by distress or impairment. However, younger individuals reporting NCP symptoms are at an increased risk for converting to a psychotic disorder [5–8], indicating a shared vulnerability. Critically, NCP individuals present with similar signs of biological vulnerability (e.g., in areas such as cognitive function), albeit in an attenuated fashion [9–12]. Taken together with the high prevalence rate and the limited potential confounds characteristic of formal psychotic disorders [12], this shared continuum of vulnerability suggests that NCP may be a highly important construct for improving the understanding of psychosis.

Motor abnormalities such as neurological soft signs, abnormal involuntary movements, and catatonia are common in formal psychosis [13]. The movement domain also represents a particularly promising area for inquiry in NCP. First, select abnormal movement signs may be unique to psychosis risk domain [13–15], and this may be helpful in isolating a weaker signal. Second, our ability to detect subtle aberrations in motor behavior which, if present, are likely to characterize populations lower on the continuum, has dramatically improved in recent years due to the more widespread adoption of instrumental assessment modalities [16–20]. Third, there is preliminary evidence to suggest that some motor deficits have already been detected in NCP, including variable force [12, 18]. Finally, and most critically, motor signs reflect abnormalities in brain circuits that are implicated in psychosis [18, 21–23]. Understanding these links, across a continuum, can yield important clues to improve the etiological understanding and to highlight new treatment targets. However, despite this promising work, to date, there has been limited research into motor function in this important area.

With respect to this last point, there is good preliminary evidence to suggest that motor behaviors linked to cerebellar-thalamic-cortical-cerebellar (CTCC) circuit dysfunction are implicated in psychosis. CTCC circuit function is critically implicated in conceptual models of schizophrenia [24, 25] and, thus far, related motor symptoms have been well recorded in populations at a clinical high risk (CHR) for transitioning to psychosis [16, 17, 21, 26] as well as in schizophrenia patients [19, 27–32]. Moreover, a recent study by our group demonstrated potential cerebellar deficits in the NCP population. Specifically, in a double-blind, crossover paradigm, NCP and control participants completed a motor-learning pursuit rotor task after cerebellar transcranial direct current stimulation at one visit, and after a sham (placebo) stimulation

at the other visit. The results indicated that, following the sham condition, NCP participants showed significantly lower rates of motor learning across trials; after the active condition, they performed at comparable rates to controls [33]. However, while this provides some support for a potential continuum of cerebellar vulnerability, currently we lack studies of motor behavior that would serve to enrich this perspective.

We and several other groups of investigators have conducted studies utilizing a postural sway paradigm, and we now have good evidence to suggest that this is a sensitive measure of CTCC circuit dysfunction [17, 21, 27, 34]. Neuroimaging research implicates the CTCC circuit in postural control, indicating that the affected cerebellar networks are related to deficits in this specific motor domain across CHR and schizophrenia populations [21, 35]. Notably, a recent study by our group denoted the cerebellum as a distinct neural substrate in the pathogenesis of psychosis and found that decreased connectivity in the CTCC circuit was associated with a larger sway area in the CHR group relative to controls [21]. This finding was the most prominent in the most challenging postural sway condition where participants were asked to keep their eyes closed and feet together. Studies assessing individuals with schizophrenia [27, 36] and schizotypal personality disorder (SPD) [36] had similar results, supporting the consistent sway pattern across the psychosis spectrum. Taken together, these findings suggest that decreasing proprioceptive and visual cues increases the challenge to the cerebellum.

If the CTCC circuit does show vulnerability across the psychosis continuum, it will also be important to build a better understanding of cognitive correlates. As noted, procedural learning has already been implicated [33], but it is important to also consider that the CTCC circuit is implicated in modulating a variety of higher-order cognitive functions including working memory [37, 38]. Correlates with sway area and cognitive performance in NCP will help to provide early building blocks for understanding how a common circuit dysfunction may contribute to a wide array of symptoms and characteristics, something that has been well established in formal psychosis with theories such as cognitive dysmetria [24, 25], but has not been investigated at the lower end of the psychosis continuum.

We aimed to examine postural sway as well as cognitive correlates in a group exhibiting high NCP and in low-NCP controls. We administered a task measuring discreet levels of postural sway across conditions designed to manipulate proprioceptive and visual cues and increasingly

challenge the CTCC circuit. Based on our previous work with CHR youth, we hypothesized that, compared to the low-NCP group, the high-NCP group would show deficits in postural control in both easier (i.e., eyes open and feet apart condition) and more difficult (i.e., eyes closed and feet together) conditions. In addition, we examined the relationship between postural control and both visual and verbal working memory in the high-NCP group, and predicted that poorer postural control will be associated with poorer performance across these tasks.

Materials and Methods

Participants

Participants (mean age 19.12 years; range 18–26 years) were recruited from the Adolescent Development and Preventive Treatment Program (ADAPT) through an undergraduate research pool. Those who participated ($n = 1,248$) completed the Launay-Slade Hallucination Scale (LSHS) [39], and the opportunity to participate in the study was offered to those scoring in the top (high-NCP) and bottom (low-NCP) 10th percentile (≥ 23 or ≤ 3 , respectively). Out of those invited ($n = 250$), 72 decided to participate. In an effort to limit sampling bias, the study description was not available during the research pool screening. Those participating were provided a detailed description of the study procedures during the consenting process. Four participants who did not complete the postural control task were excluded from all analyses. No other participants were excluded from the study. The final sample ($n = 68$) consisted of 37 participants in the high-NCP group and 31 in the low-NCP control group. Antipsychotic treatment was an exclusion criterion, and no participants reported use of antipsychotics. In the entire sample, 7.4% reported taking antidepressants, 4.4% anti-anxiety medication, 23.5% birth control medication, and 13.2% other medications.

Clinical Measures

The LSHS is a well-validated [39] and commonly used scale for identifying NCP symptoms in healthy populations [9, 40, 41]. It is a 12-item self-report scale measuring hallucination proneness, with scores ranging from 0 to 48. Participants were asked to rate hallucinatory experiences (e.g., “In my daydreams I can hear the sound of a tune almost as clearly as if I were actually listening to it”) on a 5-point Likert scale ranging from 0 (certainly does not apply) to 4 (certainly applies). Although LSHS does not assess the broad range of potential NCP experiences (e.g., unusual thought content and suspiciousness), its items reliably capture low-level, subclinical symptoms on the psychosis spectrum [42]. Furthermore, the Brief Psychiatric Rating Scale (BPRS) [43], a clinical interview designed to track changes in psychotic symptoms, was administered to rule out frankly psychotic symptoms. Scores of 4 (moderate) or higher on the BPRS was an exclusion criterion, and all participants scored below that threshold. No participants in either group were excluded based on the BPRS scores. A scale of drug and alcohol use was used to assess the frequency of alcohol use, rated as 0 (no use) to 5 (almost daily) scale, i.e., higher scores represent more frequent use.

Postural Control

Postural sway data were acquired using an Advanced Mechanical Technology Incorporated (AMTI) AccuSway force platform (Watertown, MA, USA). Participants were instructed to stand still on the force platform with their arms resting at their sides while completing four 2-min-long task conditions: (1) eyes open, open base (EOOB); (2) eyes closed, open base (EOCB); (3) eyes open, closed base (EOCB); and (4) eyes closed, closed base (ECCB). The sway conditions are designed to provide increased challenge to cerebellar function by decreasing proprioceptive information (i.e., feet together) and sensory information (i.e., eyes closed). The center of pressure (COP) was the variable of interest, and it recorded at a sampling rate of 50 Hz. We applied a 9th-order Butterworth filter with a 20-Hz cut-off frequency to isolate the low-frequency postural sway process in the recorded data. COP and the 95% confidence interval of COP area were measured using principle component analysis [44]. Higher COP area is associated with poorer postural control. As noted, we predicted that deficits are subtler in the NCP population; we thus used the easiest condition with ample sensory cues (EOOB) and the most challenging condition with significantly decreased sensory cues (ECCB) in analyses.

Cognitive Measures

The study only included a limited cognitive battery, which focused on working memory. Trained assessors administered 2 tests from the Wechsler Memory Scale (WMS)-III [45]. In the Spatial Span task measuring visual working memory, participants were asked to tap cubes on a board of 10 irregularly spaced cubes in the same order as the administrator and then in reverse order. The Letter-Number Span task, measuring verbal working memory, is orally administered; the participants were asked to remember and reorder strings of letters and numbers and repeat them to the administrator. The age- and gender-corrected scores for each test were used in the analyses, and higher scores represent higher cognitive function.

Statistical Approach

Independent t tests and χ^2 tests were used to examine possible differences between the low- and high-NCP groups in demographic and clinical characteristics. For postural sway analyses, outliers were identified a priori as values >3 standard deviations from the group mean. Across both conditions, a total of 5 outliers were removed. Four data points were removed from the low-NCP group and 1 from the high-NCP group. Considering that alcohol use can impact cerebellar function [28, 34], we controlled for frequency of alcohol use in all analyses. A 2×2 (condition $\times$ group) repeated-measures ANCOVA was conducted to examine group differences in postural sway. Post hoc univariate ANCOVAs were employed to further examine these differences. Lastly, partial correlations were used to test the predicted associations between both verbal and visual working memory and sway area in the high-NCP group. All analyses were conducted using two-tailed tests.

Results

Demographic, Clinical, and Cognitive Characteristic

The demographic, clinical, and cognitive characteristics are presented in Table 1. Independent sample t tests

Table 1. Demographic, clinical, and cognitive characteristics

	High-NCP group	Low-NCP group	Total	Group differences
Gender				
Male	17 (45.9)	16 (51.6)	33 (48.5)	ns
Female	20 (54.1)	15 (48.4)	35 (51.5)	
Total	37	31	68	
Age, years	19.03±1.5	19.23±1.56	19.12±1.56	ns
Parental education, years	15.74±1.64	15.01±3.45	15.41±2.63	ns
NCP symptoms ^a	26.62±2.97	1.81±1.05	15.31±12.66	$p < 0.001$
Letter-number span task score	47.84±7.10	47.84±7.50	47.84±7.23	ns
Spatial span task score	46.59±9.27	50.42±10.74	48.34±10.08	ns

Values are expressed as n (%) or mean $\pm$ SD. NCP, nonclinical psychosis.

^a Total score on the Launay-Slade Hallucination Scale.

and χ^2 tests revealed no significant differences in age ($t_{66} = 0.52$, $p = 0.60$), gender ($\chi^2_1 = 0.22$, $p = 0.64$), and parental education ($t_{66} = -1.14$, $p = 0.26$) between the low- and high-NCP groups. Reflective of the sampling method, an independent sample t test demonstrated that the high-NCP group (mean 26.62; SD 2.97) presented with significantly elevated NCP symptoms (i.e., sum scores on LSHS) when compared to the low-NCP group (mean 1.81, SD = 1.05) ($t_{66} = -44.29$, $p < 0.0001$). Lastly, independent sample t tests showed no group differences in the Letter-Number Span ($t_{66} = 0$, $p = 1$) and Spatial Span ($t_{66} = 1.58$, $p = 0.12$) tasks.

Sway Area Differences

A 2×2 repeated measures ANCOVA indicated a significant main effect of group ($F_{1, 61} = 4.87$, $p = 0.03$, $\eta^2_p = 0.07$) and main effect of balance condition ($F_{1, 61} = 40.22$, $p < 0.0001$, $\eta^2_p = 0.4$) (Fig. 1). Consistent with our prediction, a post hoc univariate ANCOVA revealed a significant main effect of group in the ECCB condition. The mean COP values in the high-NCP group were significantly elevated when compared to the low-NCP group ($F_{1, 63} = 5.63$, $p = 0.02$, $\eta^2_p = 0.08$). However, the COP values were not significantly different in the EOOB condition ($F_{1, 62} = 2.88$, $p = 0.1$, $\eta^2_p = 0.04$) (Fig. 1).

Associations between Sway Area and Cognition in High NCP

The partial correlations revealed that, when controlling for alcohol use, larger sway area in the ECCB condition was associated with poorer scores in the Letter-Number Span task ($r = -0.38$, $p = 0.02$) (Fig. 2) while the Spatial

Span task was not significantly correlated ($r = -0.26$, $p = 0.13$). In the EOOB condition, however, when controlling for alcohol use, the Spatial Span task was associated with postural control ($r = -0.34$, $p = 0.05$) but the Letter-Number Span task was not ($r = -0.22$, $p = 0.21$).

Discussion

To our knowledge, this the first study to examine postural control and cognitive correlates in the NCP population. We found that high-NCP individuals presented with postural instability relative to the low-NCP controls. Notably, these findings are consistent with previously identified deficits in the same motor area in the CHR [17, 21] and schizophrenia [27, 32, 36] populations. Furthermore, the degree of sway aberrations was correlated with poorer performance in the working-memory tasks. Taken together, these results provide further evidence of implications of CTCC circuit vulnerability across a continuum of psychosis. This is also in line with the cognitive dysmetria theory of psychosis, which posits that general dysfunction in sensorimotor and cognitive processes is associated with impairments in the CTCC network [24, 25].

This study provides additional support for aberrant postural control as a marker of motor-domain vulnerability, and studies examining schizophrenia and CHR populations show that balance control is largely affected. Research utilizing the same paradigm as in this study has revealed poorer postural control in these populations compared with controls across all conditions [17, 21, 27]. In addition, given that postural control is heavily reliant

Fig. 1. Sway area for high-NCP participants and low-NCP controls across the 2 balance conditions. High-NCP participants showed significantly worse postural control (greater sway) in the most challenging condition. Error bars indicate the standard error of the mean. * $p < 0.05$.

Fig. 2. Correlation between sway area in the most challenging condition (ECCB) and working memory in the high-NCP group.

on sensory input [46] and that the cerebellum plays an important role in sensorimotor integration [47, 48], postural deficits also support dysregulation in this neurological domain. Thus far, this has been noted later in the course of an illness [49, 50] as well as in psychosis-prone healthy individuals [51]. In addition, findings from a recent study indicating that aberrations in postural sway are evident in the SPD population provided additional evidence for motor deficits and affected sensory integration across the psychosis continuum [36]. Notably, the authors found that SPD participants performed significantly worse than controls, and that their postural sway abnormalities were comparable to those of participants with schizophrenia. Considering that individuals with SPD do not present with extensive functional decline in most neurobehavioral domains seen in schizophrenia [52], these findings suggest that postural deficits may be a result of a distinct psychosis risk pathway. Our findings are in line with the abovementioned research and support the notion that sensory integration could be affected across the psychosis spectrum.

As previously noted, the current postural sway paradigm is a sensitive measure of cerebellar dysfunction, as postural control deficits are more evident when the challenge to the cerebellum is increased [21, 27, 36]. Our findings indicate that the high-NCP group exhibited deficits in postural sway in the condition that most significantly challenged the CTCC circuit (i.e., when both proprioceptive and visual cues were decreased) but not in the easier condition (where cues in both domains were provided). Considering that deficits are evident across both condi-

tions in schizophrenia and CHR [17, 21, 27] but could only be detected in the more difficult one in NCP, it is likely that these aberrations change in severity across the psychosis continuum. Furthermore, this finding highlights the importance of advances in instrumental measures that can detect subtle deficits and provide more robust evidence, thereby improving our understanding of the motor domains implicated in the etiology of psychotic disorders [53].

In schizophrenia, converging evidence suggests that cerebellar dysfunction could account for some cognitive symptoms [54]. Indeed, ample research indicates that the dysfunction in the CTCC circuit is related to deficits in higher-order cognitive function including working memory [38, 55–58]. Though research on this topic is limited, motor and working-memory correlates have been reported in schizophrenia populations [59].

In this study, in the most challenging condition, larger sway area was associated with poorer performance in the verbal working memory task; in the easier condition, it was associated with the visual working memory task. Evidence suggests that verbal and spatial processing are differently lateralized [60, 61], likely due to the modality of the stimulus [62]. Therefore, these findings could also be attributed to the different information processing domains involved in the tasks. Specifically, visual working memory relies on visual sensory input. Likewise, in the EOBB condition, participants can rely on visual input, and the research suggests that more infrequent visual feedback does not result in visuomotor activation in the cerebellum [63]. Conversely, the ECCB condition and

verbal working memory do not rely on visual sensory input, and they could be affected by different cerebellar processes within the cerebellum and across a broad array of neural networks. Additionally, a recent meta-analysis revealed altered cerebellar topography in schizophrenia patients, particularly that related to working memory [38]. Therefore, it could be that different cerebellar regions are not affected significantly enough in the NCP to cause more widespread deficits. Of note, our results indicate that the 2 groups did not differ in either working memory domain, and the observed deficits were only relative to postural control; therefore, these findings should be interpreted with some caution.

Though implicated on a subtler level in the NCP group, postural sway aberrations and the cognitive correlates support the emerging evidence of the cerebellar dysfunction as implicated in the development and progression of psychosis. Overall, our study provides further evidence of the role of the CTCC circuit in the pathogenesis of psychosis. The observed deficits are consistent with the cognitive dysmetria theory, in that the potentially impacted cerebellar networks may be contributing to the postural sway deficits and the cognitive correlates [24, 25]. Therefore, while it is well-established that this theory is a valuable framework for explaining schizophrenia, it may also be useful for trying to understand the subtler deficits observed in the NCP population.

Lastly, this study presented with both strengths and limitations. The advantage of the study was the utilization of an instrumental measure of postural control which provided more reliable and discrete values than observer-rated measures [64]. However, although postural sway has been shown to be a sensitive measure of cerebellar dysfunction [17, 21, 27, 34], we did not directly measure brain abnormalities. Future research would benefit from investigating deficits in the CTCC circuit in the NCP population using neuroimaging approaches. Furthermore, although we controlled for alcohol use in all analyses, further examination of such influences in the NCP population is warranted, considering that alcohol use significantly moderates sway aberrations in individuals with schizophrenia [28, 34]. In addition, our cognitive battery was limited to the verbal and visual working memory. Considering that other studies have found that cognition is affected and associated with psychotic-like symptoms in NCP individuals [10] and continues to be impacted in CHR states, and that later conversion to a psychotic disorder is associated with more severe dysfunction [65], additional examination of cognitive function is crucial. Future studies could benefit from utilizing measures of dif-

ferent cognitive domains to establish whether cognition (in a broader sense) is impacted in the NCP population. Finally, although NCP experiences are related to an increased risk for transitioning to a formal psychotic disorder such as schizophrenia [5–8], only a small portion of these individuals will experience a psychotic outcome. Future work that longitudinally examines the progression of motor abnormalities could improve our understanding of their predictive value and role as a distinctive domain contributing to the onset of psychosis.

Our findings are largely consistent with what has been observed in CHR, SPD, and schizophrenia populations, indicating a shared vulnerability. Considering that subtle motor deficits can be detected well before the onset of psychosis, investigating them in the NCP population could provide critical insights into the progression of the noted abnormalities and their contribution to the onset of psychosis.

Statement of Ethics

Subjects gave their written informed consent. The study protocol was approved by the Institutional Review Board on human research.

Disclosure Statement

Authors have no conflicts of interest to report.

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Author Contributions

Ms. Ristanovic conceptualized the study, conducted the analyses, and drafted the manuscript under Dr. Mittal's supervision. Mr. Osborne, Ms. Vargas, and Ms. Gupta helped with data analyses, interpreting the results, and drafting the manuscript. Dr. Mittal attained the funding and provided critical revisions to the manuscript.

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