Neurological Soft Signs Predict Abnormal Cerebellar-Thalamic Tract Development and Negative Symptoms in Adolescents at High Risk for Psychosis: A Longitudinal Perspective

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Introduction: There is an emerging consensus that neurological soft signs (NSS) may not be “soft” at all but rather may reflect neuropathy, particularly in the cerebellum and thalamus. However, our understanding of connective tract abnormalities is limited, and to date, there have been no investigations examining NSS and longitudinal white matter development during the prodrome. Mapping the correlates of NSS in ultrahigh-risk (UHR) youth offers potential for highlighting a viable biomarker as well as for advancing understanding of pathogenic processes during the adolescent risk period. Methods: A total of 68 (33 UHR and 35 healthy control) adolescents were assessed with an NSS inventory, structured interviews, and diffusion tensor imaging. Fractional anisotropy (FA) of theoretically relevant cerebellar-thalamic tracts was calculated (left/right superior cerebellar peduncles [SCPs]). Twelve months later, a subset of 30 (15 UHR and 15 control) participants returned for follow-up diffusion tensor imaging/clinical assessments. Results: UHR youth exhibited elevated NSS across domains. While there were no group differences in the integrity of the SCPs at baseline, controls showed a normative increase while the UHR group showed a decrease in FA over 12 months. NSS predicted a longitudinal decrease in cerebellar-thalamic FA and elevations in negative but not positive symptoms 12 months later. Discussion: Findings of abnormal white matter development provide direct empirical evidence to support prominent neurodevelopmental theories. The predictive relationships between NSS and longitudinal cerebellar-thalamic tract integrity and negative symptom course provide insight into the role of cognitive dysmetria in the high-risk period and inform on a unique biomarker tied to core features underlying psychosis.

Key words: neurological soft signs/psychosis/prodrome/UHR/DTI/superior cerebellar peduncle/cognitive dysmetria

Introduction

Kraepelin first noted signs of neurological disturbances in his original conceptualizations of schizophrenia, and the term neurological soft signs (NSS) was first coined in the 1940s to describe nondiagnostic abnormalities in the neurological examinations of children with psychosis. Although NSS are among the earliest vulnerability markers, and closely tied to core pathophysiology of the illness (primarily negative symptoms), these neurological signs have long been conceptualized as “soft” or diffuse. In challenge to this idea, an emerging research literature suggests that NSS are indeed localizable. In a recent review, Zhao and colleagues reported that NSS are associated with atrophy and altered brain activation in several structures, including the cerebellum and thalamus. However, as studies continue to find associations between NSS and both structures, it is clear that one distinct and heretofore untested possibility is that the primary efferent white matter tracts connecting the cerebellum and thalamus (ie, superior cerebellar peduncles [SCPs]) are playing an important underlying role. Despite the promise of NSS as a vulnerability marker, to date, there has been little work to inform our understanding of the prevalence or neurocorrelates in the critical adolescent prodromal stage immediately preceding the onset of psychosis. Examining NSS in youth at ultrahigh risk (UHR) for psychosis is important as it stands to improve understanding of an elusive behavioral maker in a period with few third-variable confounds. Further, adolescence

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is characterized by substantial neuroreorganization, and abnormalities in white matter development among UHR youth are believed to contribute to a poorer course of illness. Evaluating relationship between NSS and cerebellar-thalamic tract changes over time in the UHR period can inform on a potentially viable predictive marker and also significantly influence our understanding of etiological factors underlying psychosis.

Although there have been few studies of NSS in the prodrome, a body of literature from other at-risk populations and archival reports provides an important perspective. Impairments in motor development have been observed in children who later develop schizophrenia. A study using a national child development birth cohort observed that the presence of NSS in the general population increased the odds of adult-onset schizophrenia or affective psychotic disorders. In one of the early prodromal studies (a published abstract), researchers observed elevated NSS in UHR patients when compared with healthy controls. An additional study surveying high-school students linked NSS to self-reported UHR symptoms. Since these early investigations, there has been little work done in this population.

Few studies have investigated brain correlates of NSS, although the recent years have seen an accelerated interest in this area. The cerebellum is closely involved in voluntary movement and motor coordination as well as higher order cognition, and in comparison with healthy controls, patients with schizophrenia have smaller cerebellum volumes. In addition, researchers have reported longitudinal trend-level reductions in cerebellar gray matter in a high-risk group. Within the present context, this is important, as cerebellar volume has been linked to higher NSS scores. Another important structure linked to NSS in schizophrenia patients is the thalamus, a relay station for selecting and relaying information between frontal and subcortical structures. The thalamus has also been the subject of several structural, spectroscopy, and functional studies, which indicate that smaller volumes and altered glutaminergic activity are characteristic of UHR individuals. Findings of specific cerebellar and thalamic correlations with NSS domains indicate support for cerebellar-thalamic circuit abnormalities. Yet to date, we have little understanding of potential associations with the primary connective white matter tracts comprising this circuit. Indeed, deficits in white matter tract integrity may in part explain why studies continue to have varied findings in linking NSS to these brain structures (contributing to the “soft” nonlocalized conception). The SCPs are the main efferent pathways of neural fibers connecting the cerebellum with the thalamus and cerebral cortex (linking a range of cognitive and motor functions). These tracts have been found to be abnormal in formal psychosis, but they presently have not been examined with regard to NSS or in a UHR sample.

There is converging evidence from several avenues of research to suggest that developmental factors play a role in organizing neural circuitry via age-related changes in structural elements supporting neural connectivity (ie, gray matter components supporting both intra- and interregional connectivity) and axons (ie, white matter component supporting primarily interregional connectivity). With regard to white matter development, thicker myelin sheaths, increased axonal diameter, and improved organization of tracts increase overall efficiency of the brain during adolescence. Because studies observe white matter abnormalities in adults with schizophrenia, researchers have begun to question if disruptions in this normative maturational pattern may contribute to the etiology of psychosis. There is strong evidence to suggest that white matter abnormalities are present in the UHR period linked to other biomarkers and characteristic of those UHR individuals with a poor course of illness as evidenced by transition and declining social function. Importantly, there have been no published studies among high-risk individuals designed to inform our understanding of changes in the cerebellar-thalamic system, or examining white matter with a specialized strategy such as diffusion tension imaging (DTI) at multiple developmental time points.

Within the context of the present study, we examine candidate maturational processes among UHR youth to determine if abnormal myelination during adolescence may result in aberrant conductivity affecting the cerebellar-thalamic communication, reflecting NSS and symptoms. A total of 68 young adults (33 UHR and 35 healthy controls) participated in clinical interviews, an NSS assessment, and DTI at baseline, and then a subgroup of 30 (15 UHR and 15 controls) returned for additional clinical interviews and DTI 12 months later. We predicted that UHR individuals would show elevations across domains of putative neurological signs (sensory integration, motor coordination, motor sequencing). Further, drawing on conceptual models of neurodevelopmental abnormalities in schizophrenia and evidence linking cerebellar and thalamic structures to NSS in patients with formal psychosis, we predicted that UHR youth would exhibit abnormal white matter development and that the presence of NSS would be tied to abnormalities in cerebellar-thalamic tract development and a poorer course of illness in the UHR group.

Methods

Participants

Participants were recruited at the Adolescent Development and Preventive Treatment (ADAPT) research program (see table 1 for demographics). The control and UHR participants were recruited by Internet advertising, e-mail postings, newspaper ads,
and community professional referrals. Exclusion criteria included history of head injury, the presence of a neurological disorder, lifetime substance dependence, and the presence of any contraindication to the magnetic resonance imaging (MRI) environment. The presence of an Axis I psychotic disorder was an exclusion criterion and to be included in the study, UHR individuals needed to meet for a prodromal syndrome defined as one or more of 3 Structured Interview for Prodromal Syndromes (SIPS) criteria: (1) recent onset or escalation of moderate levels of attenuated positive symptoms (n = 28), (2) a decline in global functioning over the last 12 months accompanying the presence of schizotypal personality disorder (n = 7), and (3) a decline in global functioning over the last 12 months accompanying the presence of a first-degree relative with a psychotic disorder such as schizophrenia (n = 5) (note: the numbers exceed the total group size because several subjects met for more than 1 category).

The presence of a psychotic disorder in a first-degree relative or meeting for an Axis I disorder was an exclusionary criterion for controls. The protocol and informed consent procedures were approved by the university institutional review board.

Each of the participants was assessed for NSS and symptoms although a total of 3 individuals elected not to participate in the imaging at baseline (1 UHR and 2 controls). Therefore, the analyses at baseline include all 68 participants with the exception of those comparisons involving imaging data, which include 65 subjects instead. Of the original 68 UHR and control individuals who were assessed at baseline, a period of 12 months had passed for 38 of the original participants. These participants were invited back for a 12-month follow-up imaging and symptom assessment although 4 in each group declined (21% attrition). Of the 30 who returned for follow-up (15 in each group), each participated in an imaging and symptom assessment. Negative symptoms were not collected for 1 participant in the UHR group at follow-up. Therefore, the analyses involving the 12-month time point include 30 subjects (with the exception for negative symptoms, which includes 29).

Clinical Interviews

The SIPS was administered to diagnose a prodromal syndrome at the time of screening and to follow the progression of symptoms at 12 months. This measure gauges several distinct categories of prodromal symptom domains including positive (unusual thoughts, suspiciousness, grandiosity, perceptual abnormalities, disorganized communication) and negative dimensions (social anhedonia, avolition, expression of emotion, expression of emotions and self, ideational richness, occupational functioning). A sum score for each category is used as an indicator of the respective dimensions of symptomatology. In addition, the Structured Clinical Interview for Axis I DSM-IV Disorders (SCID) was administered to rule out Axis I psychotic disorder. This measure has been demonstrated to have excellent interrater reliability in adolescent populations and has been used in other studies focusing on adolescent populations. The training of interviewers (who were advanced doctoral students) was conducted over a 2-month period, and interrater reliabilities exceeded the minimum study criterion of $\kappa \geq 80$.

Neurological Soft Signs

The Neurological Evaluation Scale (NES) is a 26-item instrument designed to measure NSS in psychotic disorders. Trained evaluators administered the scales based on the original scoring instructions, and items were scored as 0 (no abnormality), 1 (mild but definite impairment), and 2 (marked impairment). Two items

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Table 1. Participant Demographics, Symptoms, and Neurological Signs

<table>
<thead>
<tr>
<th></th>
<th>Healthy Control</th>
<th>UHR</th>
<th>Grand Total</th>
<th>Group Differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>15 (43%)</td>
<td>20 (61%)</td>
<td>35 (51%)</td>
<td>NS</td>
</tr>
<tr>
<td>Females</td>
<td>20 (57%)</td>
<td>13 (39%)</td>
<td>33 (49%)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>35</td>
<td>33</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean years (SD)</td>
<td>17.77 (2.71)</td>
<td>18.52 (2.06)</td>
<td>18.13 (2.43)</td>
<td>NS</td>
</tr>
<tr>
<td>Parent education</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean years (SD)</td>
<td>15.60 (2.86)</td>
<td>16.33 (2.03)</td>
<td>15.94 (2.51)</td>
<td>NS</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antipsychotic</td>
<td>0</td>
<td>3 (9%)</td>
<td>3 (4%)</td>
<td>$P \leq .05$</td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive: mean (SD)</td>
<td>0.69 (1.32)</td>
<td>11.55 (4.69)</td>
<td>5.96 (6.42)</td>
<td>$P \leq .01$</td>
</tr>
<tr>
<td>Negative: mean (SD)</td>
<td>0.60 (1.21)</td>
<td>10.73 (6.54)</td>
<td>5.51 (6.86)</td>
<td>$P \leq .01$</td>
</tr>
</tbody>
</table>

Note: NS, not significant; UHR, ultrahigh-risk group. Positive and negative symptoms reflect total sums from domains from the Structured Interview for Prodromal Syndromes (SIPS).
(the suck and snout reflex) were scored 0 (absent) or 2 (present). Fourteen items are assessed bilaterally. Analyses were conducted with the total NES summary score in addition to theoretically based subscales including sensory integration, motor coordination, and motor sequencing.41 Exploratory factor analyses revealed that there were no additional or different latent factors over and beyond these widely used conceptually based components.45 Raters were trained by an expert (V.A.M.) in motor phenomena in the psychosis spectrum, and these raters were kept blind to the hypotheses of this study. Following an in-depth training protocol, the interrater reliability met intraclass correlation coefficients ≥0.85.

**Diffusion Tensor Imaging**

Brain imaging was acquired on each subject using a 3-Tesla TIM Trio Siemens MRI scanner with 12-channel parallel imaging. DTI data were acquired using a diffusion-weighted echo planar scan (71 gradient directions; repetition time = 9600 ms; echo time = 86 ms; generalized autocalibrating partially parallel acquisitions parallel imaging factor 2; β value = 1000 s/mm²; field of view = 256 mm; 72 slices; 2-mm³ isomorphic voxels; 7 β0 images). Diffusion-weighted images were processed using FSL’s FDT toolbox46 and Tract-Based Spatial Statistics (TBSS).47 Images were corrected for motion and eddy current distortions. A diffusion tensor model was fitted at each voxel, resulting in fractional anisotropy (FA) images. FA images for each participant were non-linearly aligned to a 1- × 1- × 1-mm standard space FA template.48 Aligned FA images were then skeletonized, and an average FA skeleton mask was created. White matter tract regions of interest (ROIs) for the left and right SCPs were extracted from the JHU (Johns Hopkins University) white matter atlases available in FSL.49 White matter ROIs were masked with the average FA skeleton, and the mean FA values were extracted for each participant from the peduncles (see figure 1).

**Statistical Approach**

A series of *t* tests and chi-square tests were employed to examine differences between groups in continuous and categorical demographic variables (respectively). Although there is not a standard set of treatment strategies for youth at risk for psychosis, one common approach involves prescribing antipsychotic medications to those exhibiting risk signs (although they are not yet formally psychotic) as this has shown some promise.50,51 This trend of naturalistically treated UHR youth has been observed in other major recent studies.43 Because the UHR group showed significantly more antipsychotic medication use in this present investigation, dummy coded medication status was treated as a statistical covariate. Analyses were also repeated with the medication-free proportion of the sample; because this did not affect the magnitude or direction of findings, the following analyses include all of the participants. To control for subtle neurodevelopment, each of the analyses also corrected for age. ANCOVAs, controlling for age and neuroleptic medication, were utilized to determine group differences in symptoms, categories of NSS, and cerebellar-thalamic tract FA. To test for changes in white matter integrity between groups over time, we conducted 2 × 2 (time × diagnostic group) repeated-measures ANCOVAs, controlling for medication and age. Post hoc ANCOVAs were employed to follow up any significant interactions or main effects. Analyses examining correlations and predictive relationships between NSS and both imaging and symptom variables were conducted with the entire sample and with the UHR group alone to determine if any effects were specific to the UHR individuals. Partial correlations controlling for age and medication were utilized to determine associations between NSS and both white matter tracts and symptoms. A series of 3 hierarchical regression analyses were conducted with SCP (average of FA from the right and left hemispheres), positive, and negative symptoms at the follow-up assessment (time 2) as the dependent variables. For these regression equations, the respective cerebellar tract or symptom variable at the initial assessment (time 1) was entered in the first block (ie, time 1 SCP, positive, or negative symptoms). In the second block, antipsychotic medication status and age were entered as covariates. The NSS total score (assessed at baseline) was entered in the
third block as the predictor variable. With each analysis, the magnitude of \( R^2 \) change (\( \Delta R^2 \)) of the predictor variable was tested for significance. This analytic approach tests the hypotheses that NSS at baseline will predict changes in cerebellar-thalamic tract integrity and symptoms 12 months later, when controlling for corresponding baseline values as well as for age and medication.

**Results**

There were no significant differences between the 2 groups in demographic characteristics including age, \( t(66) = 1.27, P = .21 \); parental education, \( t(65) = 1.18, P = .24 \); or gender, \( \chi^2(1) = 2.41, P = .14 \). The UHR group contained significantly more individuals treated with antipsychotic medications than healthy controls, \( \chi^2(1) = 3.32, P = .04 \). As expected, the UHR group showed significantly more positive, \( F(1,64) = 65.61, P \leq .01 \); and negative symptoms, \( F(1,64) = 30.35, P \leq .01 \), when compared with controls (see table 1). This was also the case at 12-month follow-up for both positive, \( F(1,26) = 15.59, P \leq .01 \) (UHR: mean = 7.60, SD = 6.02; control: mean = 0.0, SD = 0.0), and negative symptoms, \( F(1,25) = 9.93, P \leq .01 \) (UHR: mean = 7.0, SD = 5.14; control: mean = 0.29, SD = 0.61).

**Group Differences in NSS**

ANCOVA analyses indicated significant group differences for sensory integration, \( F(1,64) = 5.07, P \leq .01 \); motor coordination, \( F(1,64) = 7.12, P \leq .01 \); motor sequencing, \( F(1,64) = 2.13, P \leq .05 \); and total NSS, \( F(1,64) = 11.17, P \leq .01 \). For each domain and total NSS, the UHR group showed significant elevations in soft signs when compared with controls (see figure 2).

**Group Differences in Structures and Tracts**

ANCOVA analyses indicated no baseline differences between UHR (mean = 0.65, SE = 0.01) and control (mean = 0.64, SE = 0.01) groups in the left SCP, \( F(1,61) = 0.79, P = .25 \). There were also no significant differences at baseline between UHR (mean = 0.64, SE = 0.01) and control (mean = 0.63, SE = 0.01) groups in the right SCP, \( F(1,61) = 0.68, P = .29 \). Repeated-measures ANCOVA analyses including 15 UHR and 15 control participants, with both baseline and follow-up imaging data, indicated a significant interaction between group and development of left SCP over a 12-month period, \( F(1,26) = 8.93, P \leq .01 \). A post hoc ANCOVA indicated that as with the baseline analyses including the larger sample of 65 (noted above), the baseline time point for the 30 participants with longitudinal data did not reflect significant group differences (although the UHR group started with slightly higher FA values), \( F(1,26) = 0.19, P = .45 \). However, at the follow-up time point, the UHR group showed significantly lower FA when compared with controls, \( F(1,26) = 5.08, P \leq .01 \). In addition, there was a significant interaction effect for right SCP, \( F(1,26) = 5.87, P \leq .05 \). Post hoc tests indicated that while there were no group differences at baseline, \( F(1,26) = 0.37, P = .38 \), at 12 months, the control group showed significantly higher FA when compared with the UHR group, \( F(1,26) = 5.35, P \leq .01 \). These findings indicate the UHR group exhibited white matter integrity comparable to controls at baseline but showed significantly lower FA.
in the left and right tracts at the 12-month time point (see figure 3).

Associations with NSS, Symptoms, and Tracts at Baseline

Partial correlations indicated that total NSS were not associated with left ($r = .02$) or right SCP ($r = .05$) FA but were strongly associated with positive ($r = .50$, $P \leq .01$) and negative symptoms ($r = .51$, $P \leq .01$) at baseline for the entire sample. For the UHR sample alone, total NSS were not tied to the left ($r = -.07$) or right ($r = -.02$) tracts or positive symptoms ($r = .21$), but there was a trend indicating an association with the negative symptom domain ($r = .27$, $P = .07$).

Baseline NSS Predict Longitudinal Changes in Cerebellar-Thalamic Tracts and Symptoms

As noted, hierarchical regression analyses were conducted on the entire sample of those participants with 2 time points to test the hypothesis that NSS measured at baseline would predict white matter tract integrity 12 months later. As shown in table 2, NSS accounted for a significant proportion of the variance (17%) in predicting a decline in white matter at 12 months ($\beta = .44$; $P \leq .01$). The direction and significance held when the regression was repeated in the UHR group alone ($\beta = -.38$; $P \leq .05$). The same strategy was used to determine if NSS would predict domains of symptoms 12 months later. Baseline NSS did not predict positive symptoms for the sample (this held when the regression was repeated for the UHR group alone).
group). Consistent with our predictions, NSS accounted for a significant proportion of the variance (6%) in negative symptoms at 12 months (β = .31, P ≤ .05), suggesting that NSS were predictive of a poorer course of negative symptomatology (the direction of findings was consistent with the UHR group but at a trend level β = .35, P = .14).

Discussion

The results of the present study provide a striking perspective on neurological dysfunction and abnormal adolescent neurodevelopment in high-risk youth. Specifically, UHR individuals indicated marked signs of neurological impairment when compared with matched control youth, suggesting that NSS precede the onset of psychosis. Further, while the high-risk youth did not show baseline differences in the integrity of cerebellar-thalamic tracts, these adolescents exhibited a longitudinal pattern that was divergent from the normative development observed in healthy controls. Finally, findings that NSS were linked to symptoms at baseline and predictive of both abnormal white matter tract development and negative symptoms 1 year later suggest that neurological signs are a viable predictive marker and may be tied to core underlying pathogenic processes.

It is widely accepted that NSS are quite common, present in up to 60% of patients with schizophrenia.44 It is possible that these neurologic signs may reflect a failure in integration within or between sensory and motor systems52 while others have suggested that NSS are the result of subcortical level dysfunction.53 Findings of NSS in recent-onset cases54 and child offspring of psychotic relatives55 as well as a number of studies reporting observations of dysfunction in other types of movement behavior in UHR youth56-62 suggest that markers of neurological dysfunction reflect a vulnerability for psychosis. Findings of deficits in integrative sensory function (eg, higher rates of bilateral extinction, impaired audiovisual integration, agraphesthesia), motor coordination (eg, abnormalities in balance and gait), and sequencing of complex motor tasks (eg, repetitive alternating hand positions) indicate that widespread neurological dysfunction also characterizes the high-risk period. Taken together, the results provide support for the theory that NSS reflect an impairment of the normal frontal-subcortical connections, which have been proposed as a fundamental pathophysiological substrates of schizophrenia.63

The UHR group indicated no baseline differences in the integrity of cerebellar-thalamic tracts from controls, but when examined in a longitudinal context, the high-risk youth failed to show the normative developmental pattern seen in the healthy controls (ie, widespread development-based increases in FA)10 and by 12 months, the groups exhibited a significant difference. Studies using a range of imaging modalities and analytic strategies also point to abnormal white matter development in other structures/tracts in UHR individuals. One DTI study in UHR adolescents, focusing on frontal ROI, detected decreased FA in the superior longitudinal fasciculus (a major fronto-parietal connection) relative to control subjects and found that when examined cross-sectionally by age, UHR participants failed to show a normal pattern of progressive FA increases in the temporal lobe white matter tracts.35 A voxel-based morphometry study found smaller white matter volume in the right temporal lobe of UHR patients, and cross-sectionally, white matter abnormalities appeared to progress to other regions in a group with schizophrenia.64 Finally, a MRI study assessed 75 UHR patients and a subset of 21 individuals who returned an additional scan at 12–18 months; the longitudinal data indicated that individuals who later developed psychosis showed a reduction in the fronto-occipital fasciculus over time.65 Interestingly, in contrast to

### Table 2. NSS Predict White Matter Integrity Decrease and Elevated Negative Symptoms 1 Year Later

<table>
<thead>
<tr>
<th>Predicting 12-mo Variable</th>
<th>Block I (Baseline)</th>
<th>Block II (Medication, Age)</th>
<th>Block III (NSS)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$R^2$</td>
<td>df</td>
<td>$F$</td>
</tr>
<tr>
<td>White matter tract $\beta$</td>
<td>Block I (white matter tract)</td>
<td>.13</td>
<td>1.28</td>
</tr>
<tr>
<td></td>
<td>Block I (positive symptoms)</td>
<td>.36*</td>
<td></td>
</tr>
<tr>
<td>Positive symptoms $\beta$</td>
<td>.59</td>
<td>1.28</td>
<td>40.85</td>
</tr>
<tr>
<td></td>
<td>Block I (negative symptoms)</td>
<td>.77**</td>
<td></td>
</tr>
<tr>
<td>Negative symptoms $\beta$</td>
<td>.44</td>
<td>1.27</td>
<td>20.79</td>
</tr>
</tbody>
</table>

Note: NS, not significant; NSS, neurological soft signs. Superior cerebellar peduncle value reflects the mean fractional anisotropy values from both left and right hemispheres; NSS reflect total score; medication includes dummy coded antipsychotics; symptoms at baseline and 12 months are from the Structured Interview for Prodromal Syndromes (SIPS).

*P < .05, **P < .01.
an earlier study of the same individuals showing decreases in cerebellar gray matter, the authors observed white matter volume increases at follow-up for both groups in this investigation.\textsuperscript{65} While the present study focused on FA instead of volume, there were differences relating to grouping (we included healthy controls but did not examine subgroups of UHR individuals) and age range (i.e., the current study only focused on adolescents and did not include adults), and we observed a longitudinal decline in white matter integrity, the collective results from both investigations do suggest that marked developmental abnormalities are occurring in the cerebellar region in UHR individuals. One interpretation of the observed decline in cerebellar-thalamic tract FA is that the developmental pattern of white matter in the UHR period is more complicated than simply a stunted level of growth and that a possible reduction in some tracts also plays a role. However, as researchers have not focused on these tracts or utilized DTI at different developmental time points in the prodromal period, future studies with larger samples will be integral in confirming the observed developmental patterns.

Previous studies of schizophrenia patients have routinely linked NSS and negative symptoms, but there has been more discrepancy with regard to the positive symptom domain.\textsuperscript{66} A review article concluded that antipsychotics may influence NSS and active psychotic symptoms are prone to interfere with assessment.\textsuperscript{66} As only several subjects were medicated (9\%) and the sample was not actively psychotic, the current link with positive symptoms and NSS domains does provide support for a genuine relationship. However, as NSS did not predict positive symptoms at follow-up, this possibility requires future investigation. For example, studies with larger samples would allow for analysis of individual NSS items, and this could help to elucidate rather particular soft signs are linked with positive symptoms.\textsuperscript{66} With regard to the negative symptom domain, the current findings are noteworthy as investigators have argued that a close link between NSS and negative symptoms (which precede illness by several years and do not oscillate)\textsuperscript{67,68} suggests that the neurological markers are also closely tied to core underpinnings of psychosis.\textsuperscript{4,69}

Findings that domains of symptoms appeared to decline over 12 months are consistent with the broader literature, which suggests improvement in a majority of UHR individuals over time.\textsuperscript{41,70–72} An important aspect of this work is to predict the course for the minority of patients who do experience increasingly severe symptoms, and it is noteworthy that baseline NSS significantly predicted an escalation with negative symptoms 12 months later. Our earlier work in UHR adolescents (in a different sample of UHR youth) found that spontaneous dyskinetic movements (a proximal marker for dysregulated striatal dopamine) collected at baseline were predictive of several domains including positive symptoms.\textsuperscript{61} The present findings provide support for an argument that the cerebellar-thalamic system dysfunction and NSS may reflect distinct pathophysiology, separable from dopaminergic conceptions of positive symptomatology. As negative symptoms significantly contribute to disability associated with schizophrenia,\textsuperscript{73} and there are few predictive markers of negative symptom course in psychosis, this possibility warrants future study.

NSS were not associated with FA at baseline, but as group differences in cerebellar-thalamic tract integrity emerged, and the UHR adolescents began to exhibit abnormalities in SCP white matter, a clear relationship became present. Specifically, we observed that elevated NSS at baseline were predictive of poorer SCP integrity 12 months later. While other neural structures are certain to play a role in contributing to NSS,\textsuperscript{74} the current results provide a unique perspective on how connective tract abnormalities are linked to these vulnerability markers. Examination of NSS with brain structure is relatively new,\textsuperscript{3} but several of the available investigations provide an important framework for interpreting this result. For example, voxel-based studies have shown that NSS are correlated with a regional loss of cerebellar matter in adults with formal psychosis.\textsuperscript{62,63} In addition, researchers have observed NSS to be related to abnormalities in the thalamus in recent-onset cases of schizophrenia.\textsuperscript{75} In a particularly relevant study, investigators observed that schizophrenia patients with elevated motor sequencing dysfunction showed a lower level of connectivity between the cerebellum and other relevant structures when compared with schizophrenia patients without NSS and controls.\textsuperscript{37}

NSS and Cognitive Dysmetria: A Neurodevelopmental Perspective

Functional studies demonstrating an involvement of the cerebellum and thalamus in higher cognitive functions such as complex narrative material, episodic memory retrieval,\textsuperscript{76} and deficits in motor behavior, as well as findings linking neurologic signs to cerebellar atrophy\textsuperscript{8} support a conception of widespread cerebellar-thalamic-based dysfunction in patients with schizophrenia. Based on this evidence, the cognitive dysmetria model hypothesizes a disruption in a cortico-cerebellar-thalamic-cortical circuit leading to impaired sequencing and coordination of mental process, manifested in characteristics associated with psychosis.\textsuperscript{24,77} As this theory has not been tested in UHR youth or evaluated in a developmental context, the present findings linking NSS to cerebellar-thalamic tract development provide a good opportunity.

A diathesis-stress conception of psychosis suggests that an early vulnerability (due to interacting genetic and prenatal factors) manifests in subtle ways throughout the premorbid period until adolescence, when environmental stressors (chronic and acute stress, substance abuse, familial environment) and both normative and pathological neuromaturational factors (dendritic arborization, hormone changes, white matter developmental abnormalities) interact to
unmask the vulnerability, leading to a prodromal period (characterized by declining cognitive and psychosocial function, as well as the emergence of attenuated positive symptoms) and eventually the transition to formal psychosis.

The developmental pattern of NSS is intriguing as prior evidence, as well as results from the present study, suggests that it fits within this framework. First, preterm cohort studies have shown that neonatal prematurity is associated with abnormal neural development, but when individuals at genetic risk are exposed to obstetric complications, they express even greater levels of neurological abnormalities, suggesting a gene-environment interaction. In support of this notion, increased rates of neurological dysfunction are seen in unaffected offspring of mothers with schizophrenia and the number of abnormalities appears to be linked to genetic proximity of the unaffected relative to the probands. However, the environment is also important as patients with schizophrenia have more neurological signs than their unaffected first-degree relatives and monozygotic twins. During adolescence, an interesting pattern emerges; specifically, NSS appear to decrease in healthy populations but not in adolescents with formal psychotic disorders. However, until recently, it has been unclear how these factors appear in the high-risk period or how they may reflect pathogenic processes underlying an eventual transition to psychosis. One possibility is that NSS are reflecting a subtle cerebellar-thalamic vulnerability that becomes increasingly strained during the progression of adolescence. As a dysfunctional cerebellar-thalamic system emerges, the progressive cognitive deficits and motor abnormalities characteristic of the prodromal period may in fact reflect, in part, emerging cognitive dysmetria. Further, our observation that NSS predict a longitudinal increase in negative symptoms suggests that neurological markers are indeed reflective of underlying factors driving the course of illness.

While the viability of NSS in predicting ultimate transition to psychosis remains an empirical question, studies of other at-risk populations suggest potential. As noted, several archival studies have suggested that children who later go onto develop schizophrenia show signs of neurological vulnerability. Notably, in a study utilizing a genetic high-risk sample (individuals aged 16–24), researchers observed that the high-risk youth showed elevated sensory integration deficits when compared with healthy controls, although there was little difference between those at-risk participants showing and not showing psychotic symptoms.

**Limitations**

In the past, results from NSS studies have been inconsistent because of low-resolution scanning, heterogeneous groups of patients, and a series of extra variable confounds inherent to patients with schizophrenia. While the present study aimed to correct for a number of these issues by using high-resolution scanning, controlling for antipsychotics, screening for head injury, benefiting from a population that is not confounded by active psychosis or advanced aging, and using expert coding, there are still a number of noteworthy limitations. First, although theoretical conceptions and empirical studies have stressed the cerebellar-thalamic network as strongly tied to NSS, other structures and tracts are certainly to play a role. Future studies including whole brain analyses and additional indices of diffusivity are certain to provide a more thorough perspective. Second, while the present sample size is comparable or larger than other DTI studies in this population (ie, key papers have ranged from 17 to 37), only a proportion of the baseline sample was invited back for a 12-month follow-up at the time of writing this report. Third, while patients with psychosis score higher than individuals with other mental illnesses, NSS have been also observed in children with behavioral and learning difficulties and in children following premature birth, low birth weight, meningitis, and malnutrition. Higher powered studies, which can control for comorbidities common to the prodrome (eg, affective disorders), and studies that include other psychiatric control groups are needed to ascertain specificity. Fourth, while the present study utilized a novel imaging modality, other methods are necessary for explaining how functional abnormalities and deficits in neuronal populations are also contributing to putative neurological signs. Finally, we used a gold standard NES scale, but alternative scales and scoring procedures are used to equal effect. Similar to current NIMH (National Institute of Mental Health) initiatives, we recommend an organized effort to draw upon the available research literature to clarify biological correlates and develop standardized terminology and assessment procedures for markers of neurological dysfunction across psychiatric illnesses.

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