Neuroimaging Markers of Resiliency in Youth at Clinical High Risk for Psychosis: A Qualitative Review

Teresa Vargas, Katherine S.F. Damme, Arielle Ered, Riley Capizzi, Isabelle Frosch, Lauren M. Ellman, and Vijay A. Mittal

ABSTRACT
Psychotic disorders are highly debilitating and constitute a major public health burden. Identifying markers of psychosis risk and resilience is a necessary step toward understanding etiology and informing prevention and treatment efforts in individuals at clinical high risk (CHR) for psychosis. In this context, it is important to consider that neural risk markers have been particularly useful in identifying mechanistic determinants along with predicting clinical outcomes. Notably, despite a growing body of supportive literature and the promise of recent findings identifying potential neural markers, the current work on CHR resilience markers has received little attention. The present review provides a brief overview of brain-based risk markers with a focus on predicting symptom course. Next, the review turns to protective markers, examining research from nonpsychiatric and schizophrenia fields to build an understanding of framing, priorities, and potential, applying these ideas to contextualizing a small but informative body of resiliency-relevant CHR research. Four domains (neurocognition, emotion regulation, allostatic load, and sensory and sensorimotor function) were identified and are discussed in terms of behavioral and neural markers. Taken together, the literature suggests significant predictive value for brain-based markers for individuals at CHR for psychosis, and the limited but compelling resiliency work highlights the critical importance of expanding this promising area of inquiry.

Keywords: Biomarker, Clinical high risk for psychosis, Magnetic resonance imaging, Neuroimaging, Resilience, Schizophrenia

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Psychotic disorders represent a massive public health cost (1) and are highly debilitating, characterized by a chronic course and substantial diversity in clinical manifestations (2,3). A sizeable portion of individuals who go on to be diagnosed with a psychotic disorder experience a “prodromal” phase before illness onset (4–6). Research on youth at clinical high risk (CHR) for developing psychosis therefore aims to identify individuals at high risk of transitioning. CHR individuals can present with attenuated psychotic symptoms, short limited psychotic symptoms, or genetic risk accompanied by functional or cognitive decline (5,7). The approach is valuable in informing and implementing prevention and intervention treatments at the individual and public health levels and provides insight into the pathogenesis of the illness (allowing insight before the onset of many confounding factors associated with illness onset, such as use of antipsychotics and lifestyle changes).

Identifying markers that aid in the identification, prediction of clinical course, and treatment efficacy of CHR individuals is critical from a prevention and intervention standpoint (8,9). Despite the prominence of brain research in CHR samples (10), brain-based risk and protective markers have not been recently reviewed. In addition to denoting risk and resiliency, neural markers have the strong potential to aid in identifying mechanistic determinants and inform conceptual understanding (11). Investigating protective neural markers occurring with simultaneous exposure to heightened risk factors for illness could help to identify those with the greatest need for care and provide clues for potential targets for treatment and preventive efforts (12–14).

We offer an overview of brain-based risk and protective markers in the CHR literature to give perspective on where the field currently stands along with future directions. Possible resiliency factors will receive the most discussion, as the research has thus far been very limited in this regard. The first part of the review will center around briefly summarizing recent reviews and discussion concerning CHR risk markers. The second part of the review will discuss resiliency markers, with special attention to cognitive, behavioral, and biological markers related to brain abnormalities. Taken together, the review aims to critically discuss neurological neural marker work in CHR populations and offer synthesis
and future directions on understanding resiliency and protective factors.

**RISK MARKERS**

Compared with protective factors, neural markers of risk have been studied much more extensively (10). Risk markers have often been identified through comparisons including nonclinical, non–help-seeking comparison groups (15). For example, a voxel-based meta-analysis of CHR neural markers found reductions in CHR gray matter volume compared with controls in right superior temporal gyrus, left precuneus, left medial frontal gyrus, right middle frontal gyrus, bilateral parahippocampal/hippocampal regions, and bilateral anterior cingulate (16). Another quantitative review using activation likelihood estimation found that compared with controls, CHR populations showed dysfunction in right inferior parietal lobule, left medial frontal gyrus, left superior temporal gyrus, and superior frontal gyrus (17). These reviews have given the field substantial insight and clarified key candidate pathogenic mechanisms; however, there are limitations to establishing risk markers through comparisons with control groups that are often nonpsychiatric and non–help seeking. Given the exceedingly high incidence of comorbid diagnoses in CHR groups (4,5,18), it is unclear whether neural markers assessed in this regard are capturing general risk for comorbid psychopathology rather than risk for psychosis specifically.

Alternatively, recent reviews have focused on neural markers predicting transition to a psychotic disorder (19–22). One meta-analysis found decreased prefrontal, cingulate, insular, and cerebellar gray matter volume in those that transitioned, along with reduced activation in prefrontal cortex, reduced neuronal density, and increased membrane turnover in frontal and cingulate cortex (20). A qualitative review, in turn, identified progressive gray matter loss, altered white matter integrity, and anomalous functional connectivity as solid predictors of transition (19). To build on the literature on transition outcomes and neural markers, which has been essential to our understanding of CHR manifestations, a valuable future direction will be to expand from focusing on transition to mapping neural markers to symptomatology independently of transition outcomes; this focus has been less prevalent in the literature. Tracking neural markers, symptomatology, and functional outcomes regardless of transition status will be increasingly beneficial in determining degrees of risk and vulnerability, possibly aiding in parsing out heterogeneity in psychosis symptom presentation. Table 1 and Figure 1 provide an overview of the literature tracking neural markers and attenuated symptomatology.

**CONTEXTUALIZING PROTECTIVE FACTORS/RESILIENCY MARKERS IN CHR**

Among those exposed to illness risk factors, potential protective or resiliency factors can be characterized as biomarkers that relate to the development of healthier outcomes or illness remission (12–14). Within CHR research, identifying protective factors is a nascent complex and multifaceted undertaking. A recent systematic review of 20 years of CHR literature identified risk and protective factors using empirical criteria (23). Only higher attenuated positive symptoms, lower global functioning, and higher negative symptoms showed evidence for association with transition to psychosis. That review highlights the highly heterogeneous nature of CHR research and calls for expanding the focus of risk and resilience beyond predicting transition to a psychotic disorder. This is especially relevant given that lifetime presence of CHR criteria maintains vulnerability across a variety of domains, regardless of conversion status (4,5,18). There is much to be gained from conceptualizing resilience outside of dichotomizing converters versus nonconverters (which has the setback of treating nonconverters as “error variance,” failing to account for psychosis risk). A growing field focusing on CHR persistence (symptoms that remain constant/do not increase in severity) and remission allows us to undertake a much-needed dimensional perspective that has potential to shed light on protective markers for psychosis spectrum symptomatology. Recent investigations undertaking such approach have yielded insights into types of biomarkers. Given the relative paucity of CHR research on protective markers, this section will first borrow from a strong body of research from nonpsychiatric populations to highlight viable resiliency markers. In addition, the broader schizophrenia spectrum disorders literature will be incorporated, as some resiliency work has already been undertaken within the psychotic disorder literature, thus facilitating more direct comparisons between psychosis spectrum disorders and CHR individuals. Then, CHR investigations that have yielded insight into resiliency markers will be discussed. To make the best use of this smaller body of resilience research, that section will incorporate discussion of behavioral resiliency markers as well, with the primary focus remaining on brain-based resiliency research.

**Demographic and Behavioral Resilience Markers**

Investigations of resilience in the face of exposure to adversity have identified demographic factors such as gender, age, race, and education, along with environmental factors including trauma exposure/life stressors, income change, social support, and parenting resources, and individual differences such as cognitive function and perceived efficacy (13,24,25). Findings have also characterized resilience as a complex and perhaps elusive construct that can be achieved through a large variety of pathways (12,14).

Within schizophrenia, general efforts to define resilience have spanned use of self-report resiliency scales along with outcomes relating to better illness course and functioning (26,27). For example, studies have characterized self-esteem, positive self-appraisals, and positive mood experiences as protective factors (28–30). Relationships between internalized stigma and global functioning have been found to be mediated by self-reported resilience (31). Other studies have focused on internal and external protective factors affecting duration of untreated psychosis and symptomatology, including psychological, social, and community resources, as well as problem solving, behavioral strategies (32), and personality characteristics (33). Research explicitly focusing on operationalizing resilience in CHR populations has been relatively sparse, though studies have reported favorable symptom profiles for those that self-report higher resilience, along with lower self-reported resilience in CHR converters (34,35). Higher
### Table 1. Sampling of CHR for Psychosis Investigations Denoting Risk Markers and Relationships With Clinical Outcomes

<table>
<thead>
<tr>
<th>Imaging Modality</th>
<th>Illustration and Source</th>
<th>Utility</th>
<th>Neural Marker Predicting Illness Course in CHR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Structural MRI</strong> (Gray Matter)</td>
<td><a href="#">Image</a></td>
<td>Measures gray matter features, indexing factors such as neural structure, development, and environmental and genetic influences</td>
<td>Decreased prefrontal, cingulate, insular, and cerebellar gray matter volume ( (20) ). Baseline cortical thickness in right lateral and medial temporal cortex and left insular cortex ( (125) ); insular volume ( (126) ). Inversion of left ventral posterior hippocampus ( (96) ) and reduced parahippocampal volume ( (127) ). Baseline pituitary volumes ( (128) ). Gray matter reduction in right superior frontal, middle frontal, and medial orbitofrontal ( (129) ). Reduced baseline volume in frontal, temporal, posterior, and cingulate regions ( (130) ).</td>
</tr>
<tr>
<td>Structural MRI (White Matter)</td>
<td><a href="#">Image</a></td>
<td>Measures white matter features, indexing factors such as myelination, which can inform understanding of efficiency of signal transmission among regions and neural networks</td>
<td>Increases in thalamomotor tract FA ( (131) ). Reductions in frontal FA ( (132) ). Increases in inferior fronto-occipital fasciculus, anterior thalamic radiation, superior longitudinal fasciculus, and corticospinal tract FA ( (133) ).</td>
</tr>
<tr>
<td><strong>Functional MRI</strong> (Resting-State)</td>
<td><a href="#">Image</a></td>
<td>Estimates how regions within a network relate intrinsically or on a “trait” level (without the addition of a specific task or behavior)</td>
<td>Dissimilar functional network organization ( (134) ). Aberrant structural covariance in salience, executive control, auditory, and motor networks ( (135) ). Reduced activation in prefrontal cortex ( (20) ). Reduced insula connectivity ( (136) ). Altered midbrain-prefrontal connectivity ( (137) ). Altered cingulate topological features ( (138) ). Thalamic dysconnectivity ( (139) ). Altered connectivity in dorsal anterior cingulate cortex, midcingulate cortex, supplementary motor area, and mesial superior frontal gyrus ( (140) ). Cerebello-thalamo-cortical hyperconnectivity ( (141) ).</td>
</tr>
<tr>
<td><strong>Functional MRI</strong> (Task-Based)</td>
<td><a href="#">Image</a></td>
<td>Estimates brain activity co-occurring with certain behaviors and cognition</td>
<td>Increased activation in bilateral prefrontal cortex, brainstem (midbrain/basilar pons), and left hippocampus and greater midbrain-prefrontal cortex connectivity during verbal fluency task ( (137) ). Greater activation in superior temporal gyrus, caudate, and left inferior frontal gyrus during language processing task ( (142) ). Less activation in prefrontal cortex, precuneus, and temporal lobes during theory of mind task ( (143) ).</td>
</tr>
</tbody>
</table>

*Used with permission from \( (129, 128, 133, 134, 135, 136, 137, 138, 139, 140, 141, 131, 132) \).*
Neural Resilience Markers in CHR Youth

Table 1. Continued

<table>
<thead>
<tr>
<th>Imaging Modality</th>
<th>Illustration and Source</th>
<th>Utility</th>
<th>Neural Marker Predicting Illness Course in CHR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magnetic Resonance Spectroscopy</td>
<td></td>
<td>Measures metabolite concentration changes indexing alterations in neurochemical mechanisms</td>
<td>Reduced neuronal density, and increased membrane turnover in frontal and cingulate cortex (20). Lower medial prefrontal GABA levels (144). Higher striatal glutamate levels (145,146). Lower thalamic glutamate levels (147).</td>
</tr>
<tr>
<td>Arterial Spin Labeling</td>
<td></td>
<td>Indexes cerebral blood flow, providing regional and temporal specificity to neural markers</td>
<td>Increased hippocampal rCBF (148). Increased pallidum rCBF (149). Increased striatum rCBF (150).</td>
</tr>
</tbody>
</table>

CHR, clinical high risk; FA, fractional anisotropy; GABA, gamma-aminobutyric acid; GSH, glutathione; L, left; nt, not transitioned; R, right; t, transitioned; tCHo, total choline; tCr, total creatine; MDMR, multivariate distance matrix regression; MRI, magnetic resonance imaging; ppm, parts per million; rCBF, resting cerebral blood flow; SFG, superior frontal gyrus; UHR, ultra-high risk.

psychosocial functioning at baseline was found to predict remission (6), along with lower attenuated positive symptoms, and use of antipsychotics and anxiolytics (36).

As noted earlier, nonpsychiatric and schizophrenia studies were used to classify main domains that affect or could be affected by resilience. First, general imaging findings related to resilience in CHR will be discussed. Then, developed domains, including cognition, emotion regulation, allostatic load, and sensor/sensorimotor function, will be discussed in behavioral terms to frame the ensuing discussion of corresponding neural markers (Table 2; Figure 2).

**General CHR Imaging Literature Touching on Resilience**

There are several noteworthy findings in CHR samples that include neural markers and touch on resilience but do not fit into the above-referenced 4 domains identified by the outside literature survey. For example, cortical abnormalities have served as candidates for CHR protective factors (23). One study found smaller brain surface area in CHR populations with persistent/deteriorating symptomatology compared with CHR populations with partially/fully remitted symptomatology (37). Larger cortical surface area within the left hemisphere also has been observed in CHR individuals that go on to exhibit resilient outcomes (38); the observed specificity to surface area poses number of cellular columns as a putative protective factor (39).

**Neurocognition Resilience Markers**

Intact neurocognition and executive function (partially due to executive function associations with greater self-control/executive function, which constitute robust protective factors) have specifically been associated positively with dispositional resilience in vulnerable populations (40,41). A phenomenon deemed “skin-deep resilience” has been identified, whereby ostensibly resilient outcomes in the face of adversity relate to self-control/executive function (42) while co-occurring with ensuing risk-factors for long-term adverse health outcomes, suggesting that resilience can take its toll on physical health (43-45). Nonpsychiatric studies highlight the critical importance of both considering executive function as a protective factor and measuring risk and resilience in tandem, as they can interrelate in meaningful ways. Studies have found relationships between increased self-reported resilience and decreased cognitive impairment across populations, including individuals with schizophrenia and nonpsychiatric groups (46). Within psychotic disorder populations, efforts to identify brain-based biotypes independent of clinical features have shown that intact executive function and overall cognitive performance co-occurs with less severe manifestations of clinical psychosis (4). Studies clustering psychotic disorder groups according to clinical features have found consistent results regarding cognitive function and symptom severity, highlighting the importance of cognitive function to conceptualizing protective factors in psychosis spectrum populations (3).

Regarding CHR populations, promising evidence has pointed to better cognitive performance at baseline among CHR individuals whose symptoms went on to remit (47); semantic fluency significantly improved in remitters over 2 years while declining in nonremitters (47). Another investigation found that groups with symptoms that remitted or remained constant improved significantly over time on social cognition (theory of mind and social perception) (48). Given promising preliminary evidence, future studies could benefit from considering cognitive performance over time as a protective factor within CHR groups, especially in executive function domains.
Neural Biomarkers Related to Neurocognition and Executive Function. Nonpsychiatric neuroscience studies aid in illuminating relationships between executive neural networks and resilience. For example, a recent investigation observed a relationship between higher neighborhood murder rate and greater cardiometabolic risk. However, in youth with greater central executive network resting-state connectivity, the relationship between greater neighborhood murder rate and

| Table 2. Clinical High Risk for Psychosis Investigations of Putative Neural Protective/Resilience Markers |
| Domain | Illustration and Source | Finding |
| Overall/General | Smaller brain surface area (37). Larger cortical surface area within the left hemisphere (38). |
| Neurocognition and Executive Function | Greater volume, thickness, and surface area among frontal regions, including cingulate (38). P300 amplitude differences not found (53). |
| Emotion Regulation | Increased amygdala and prefrontal activation, as well as stronger negative amygdala-prefrontal functional connectivity during emotional faces task (54). |
| Allostatic Load | Increase in activation in anterior cingulate and right parahippocampal gyrus (77). Decreases in left hippocampal rCBF (98). |
| Sensory and Sensorimotor Function | Increase in white matter integrity of the corpus callosum (116). Higher between-network connectivity (among language, dorsal attention, cerebellar, sensorimotor, and salience networks) and more typical modular connectome organization (115). Greater volumes in temporal, parietal cortex, and corpus callosum regions (38). Greater auditory mismatch negativity amplitude (118). Greater P300 novel amplitude (119). |

NR, nonresilient; R, resilient; rCBF, resting cerebral blood flow; UHR, ultra-high risk.
increased cardiometabolic risk was not present; the moderation suggests that central executive network connectivity could serve as a protective biomarker for at-risk populations (49). The central executive network facilitates self-control and inhibition as well as relating to reappraisal and suppression (60).

In terms of neural markers related to executive function and neurocognition among schizophrenia studies, reduced resting-state connectivity in prefrontal networks was found to confer greater risk for the illness (51). Regarding structural imaging and prefrontal cortical folding, one investigation found that specific cortical folding patterns within the orbitofrontal cortex could serve as protective factors given their decreased incidence in first-episode psychosis subjects compared with control participants (52). Among CHR investigations, high-risk individuals classified as resilient (owing to symptom improvement over a 6-year period) had larger baseline frontal volumes, along with greater cortical surface area and thickness in frontal regions (38). Regarding event-related potentials, however, P300 amplitude, a late cognitive component indexing working memory updates of change and attention, was not found to predict symptom remission in CHR (53). Especially given current CHR evidence, further studies would be valuable in determining the possible protective role of neural executive neurocognitive function and structure in CHR individuals.

**Emotion Regulation Resilience Markers**

Nonpsychiatric studies have long highlighted emotion regulation—the ability to efficiently modulate emotions and effectively process negative/disruptive emotions—as a pathway to resilience in the face of adversity (12,54,55). Schizophrenia investigations also have found effective emotion regulation to relate to reduced stress sensitivity (56), less severe hallucinations (57), and persecutory delusions (58), as well as to better psychosocial and overall clinical outcomes (59,60). Nonetheless, a recent meta-analysis of individuals with psychotic disorders found that while maladaptive emotion regulation strategies were associated with positive symptom severity, this was not the case with use of adaptive emotion regulation strategies (61). Thus, it is possible that adaptive emotion regulation serves as a protective factor before illness onset, rather than after illness onset.

Although the literature on CHR and resilient/protective outcomes stemming from emotion regulation is quite limited, there is some promising evidence from nonclinical psychosis investigations. One study found that youth who used reappraisal reported less distress from psychotic experiences (62). That study also found reappraisal to mediate the relationship between personality characteristics and psychotic experiences (62). More peripherally, cognitive therapy, which has a strong emphasis on reappraisal skills (63), has been shown to reduce both positive and negative symptomatology in CHR and first-episode psychosis populations (64–66). Although it seems that maladaptive emotion regulation is likely linked to symptomatology in CHR populations (60,67–69), it is unclear whether implementing adaptive emotion regulation interventions and treatment goals at this stage would definitively serve as a protective factor; this is a valuable future direction for research.

**Neural Biomarkers Related to Emotion Regulation.** In nonpsychiatric studies, modulating amygdala reactivity and recruiting prefrontal control regions has been associated with effective emotion regulation among youth exposed to risk factors such as adverse childhood experiences and maltreatment (64,70–72); in these individuals, reduced amygdala activation and recruitment of frontal regions during regulation of negative affect has been interpreted as efficient/adaptive emotion regulation (70). Similarly, schizophrenia studies indicate resilience to self-stigma related to functional neural correlates of emotion regulation (54,73). Reduced symptomatology has also been linked to normalization of prefrontal-limbic activation due to cognitive therapy involving reappraisal training (74,75).

Within CHR populations, CHR individuals who remitted performed with greater accuracy during an emotional faces task at baseline (76). During the emotional faces task, CHR participants who remitted, similarly to control participants, showed increased amygdala and prefrontal activation as well as stronger negative amygdalar-prefrontal functional connectivity (76). Another investigation tracked CHR symptomatology longitudinally, finding that clinical symptomatology and functional improvement related to a longitudinal increase in activation in the anterior cingulate and right parahippocampal gyrus (54); change in anterior cingulate response was directly correlated with improvement in functioning (77). Future investigations will be needed to understand the extent toward which emotion regulation could relate to these neural presentations.

**Allostatic Load Resilience Markers**

Allostatic load refers to consequences of chronic exposure to increasing/Fluctuating neural/neuroendocrine responses due to chronic stressful environmental challenges (78). Within nonpsychiatric populations, youth under conditions of high cumulative socioeconomic status–related risk who displayed resilient outcomes of high psychosocial competence also displayed indicators of presumed high allostatic load compared with youth at low socioeconomic status–related risk (42). These results are consistent with another investigation of youth from disadvantaged neighborhoods (79).

Regarding allostatic load and hypothalamic-pituitary-adrenal axis function, elevated diurnal cortisol due to chronic stress exposure in individuals at risk for or diagnosed with a psychotic disorder has been associated with a loss of ability to respond adaptively to acute stress, resulting in a blunted cortisol response to acute psychosocial stress (80–82). On the other hand, in healthy or at-risk individuals exhibiting a resilience biomarker, “normal” diurnal cortisol is associated with a preserved capacity for response to acute stress (80–82). Consistent with this notion, an investigation comparing cortisol levels in CHR remission and psychotic transition groups found that subjects in the remission group had lower baseline cortisol compared with those that converted (83). Given that lower stress exposure has been directly associated with less severe positive symptoms (84), allostatic load remains an essential consideration to models of resilience and protective factors.
Neural Biomarkers Related to Allostatic Load. In addition to being intricately associated with risk and resilience to psychotic disorders (85,86), allostatic load is liable to affect widespread neural systems subsuming stress sensitivity (87). Protective or resiliency factors relating to allostatic load could involve capitalizing on developmental brain plasticity. Regions with greater plasticity, or with protracted developmental trajectories, that are sensitive to stress exposure and involved in the stress response could be particularly relevant targets (e.g., hippocampal/medial temporal regions, along with certain prefrontal regions) (88–93). In psychotic disorder populations, findings have been limited, although indicators of greater allostatic load have been linked with reduced overall cortical thickness and white matter integrity (94,95).

Among CHR studies, there is some intriguing preliminary evidence pointing toward future targets for resiliency. For example, our group found significantly greater hippocampal shape inversion in CHR individuals with deteriorating symptomatology, compared with CHR individuals whose symptomatology improved or stayed the same, along with a trend level difference in CHR individuals who showed increasingly impaired tolerance to normal stress at follow-up (96). Another longitudinal investigation found that CHR individuals who remitted did not exhibit decline in hippocampal CA1 volume over time (97). A study comparing groups based on changes in symptomatology over time found that compared with individuals at CHR with partially or fully remitted symptoms, 12- to 17-year-olds at CHR with persistent or increased symptoms showed smaller surface area in rostral anterior cingulate, lateral and medial prefrontal regions, and parahippocampal gyrus. Longitudinal decreases in hippocampal resting cerebral blood flow have also been observed in CHR remitters (98). Future investigations examining relations between clinical symptomatology, impaired stress tolerance, and allostatic load will aid understanding of protective factors.

Sensory, Motor, and Sensorimotor Function Resilience Markers

Aberrant sensory integration and motor functioning serve as indices of vulnerability across psychiatric conditions (99,100). Neurological soft signs, which index facets of aberrant sensory and motor processing (101), are particularly robustly observed in psychosis spectrum populations (99,101–104). Within psychotic disorder individuals, a meta-analytic synthesis suggests that symptom remission and functional outcomes relate to reductions in sensorimotor dysfunction (102,105), suggesting that intact sensorimotor function could serve as a protective factor in individuals with a psychotic disorder.

CHR investigations exploring protective factors surrounding sensory and motor functioning have been particularly scarce. One investigation did not observe differences in motor or perceptual disturbances between CHR remission, persistence, and progression groups (106). While indexes of sensorimotor function such as neurological soft signs have been found to relate to symptomatology in CHR (101), they have not been centrally explored in the context of remission or protective factors. Notably, one study clustered CHR individuals into motor performance profiles (including dyskinesias, psychomotor slowing, and neurological soft signs) (107). The cluster that was characterized by healthy motor performance exhibited less impaired cognitive function and negative symptomatology compared with clusters with impaired motor performance (107). Given the promising preliminary evidence and the key role of motor abnormalities in the pathogenesis of psychotic disorders, exploring sensory and motor function in the context of CHR persistence/remission and resilience will be a valuable future direction.

Neural Biomarkers Related to Sensory, Motor, and Sensorimotor Function. Sensory and motor symptoms have long been conceptualized as transdiagnostic markers of neural vulnerability (108–111). However, research explicitly aiming to identify resilience markers within the sensory/sensorimotor domain has been sparse. One investigation observed altered left hemisphere occipitotemporal connectivity in patients with childhood-onset schizophrenia and unaffected siblings. For unaffected siblings, the aberrant connectivity had normalized by mid-adolescence, indicating a possible sensory processing resilience endophenotype (112).

Regarding sensory processing, neural auditory information processing assessed with event-related potential data has been associated with both functional outcomes and negative symptoms in individuals with a psychotic disorder (113). In terms of motor function, striatal subregional shape abnormalities have been observed in childhood-onset schizophrenia compared with healthy control subjects. These striatal shape abnormalities were partially shared by unaffected siblings, suggesting a resilience endophenotype (114).

Within the CHR literature, a study using functional connectivity to predict symptom progression outcomes in CHR individuals found that higher between-network connectivity (among language, dorsal attention, cerebellar, sensorimotor, and salience networks) and more typical modular connectome organization predicted improvement in clinical outcomes and symptomatology (115). Another study explored resilience structural neural biomarkers defined by CHR outcome 6 years later (38). CHR individuals classified as resilient showed greater volumes at baseline in temporal cortex, parietal cortex, and corpus callosum, regions underlying auditory processing and sensory and sensorimotor integration (38); these differences remained stable over time. More specifically, and consistent with the above gray matter findings, a study showed positive symptom improvement over time correlated with an increase in white matter integrity of the corpus callosum (116); findings in corpus callosum across gray and white matter metrics could underlie more integrated cognitive and sensorimotor processing, serving as a protective marker (110,117). Other studies explored sensory processing using event-related potential data. Auditory mismatch negativity amplitude, which relates to preattentive auditory processing, significantly predicted both remission from CHR symptomatology and general functioning at 6-year follow-up (118). Reduced P300 novel amplitude, indexing impaired salience processing, was also recently found in individuals at CHR who did not remit compared with those who remitted (119). As it
stands, more longitudinal investigations integrating across multiple imaging modalities are warranted, which would help to solidify our understanding of possible sensory/sensorimotor resilience markers.

CONCLUSIONS

Decades of CHR research have yielded a wealth of fruitful information on neural risk markers, which have been summarized across several reviews (10,16,17,19–22). Future investigations will benefit from tracking attenuated symptomatology along neural markers despite conversion status. To frame an emergent literature and highlight a promising area of focus, behavioral and brain-based resiliency markers were conceptualized across 4 domains and reviewed among available CHR studies on symptom remission and persistence. Domains of executive function and neurocognition, emotion regulation, allostatic load, and sensory and sensorimotor function were delineated with the aid of existing nonpsychiatric and psychotic disorder literature. Although neural markers may not appear as widely scalable or translatable as behavior, they are critical tools to validating scalable behavioral markers and are necessary for spearheading efforts to parse out etiological and pathophysiological heterogeneity in psychotic disorders (2). As a consequence, neural markers also hold immense promise for precision medicine approaches to treatment and prevention (120,121). As such, future resiliency research would benefit from integrating behavioral and neural markers when envisioning CHR resilience profiles.

In addition to these summary points, we hope to frame future directions in light of what was reviewed. CHR risk marker research has often centered on predicting conversion to a psychotic disorder (23). While these efforts are necessary, the present review proposes that to maximize progress in the field, the scope ought to be broadened from considering conversion as the unique determinant to tracking attenuated positive symptomatology over time and dedicating greater consideration to those whose symptoms remit versus those whose symptoms persist or progress (along with greater attention to other outcomes, such as functioning and neurocognition). Comparisons based on conversion status can limit sample sizes and suffer from limitations related to false negatives (5,7). Furthermore, psychosis symptoms can be debilitating regardless of conversion status (122,123). Critically, as highlighted throughout this review, resilient-appearing outcomes can belie risk-conferring components owing to factors such as wear-and-tear of biological and neurological systems in light of exceedingly high demands. Conversely, poor outcomes signaling risk factor exposure could contain underlying protective/resilient components that preserve the integrity and foundations of biological/neural systems under increased demands (51,124). Thus, to understand risk, it is necessary to understand resilience, as it is necessary to grasp and identify existing protective factors in order to conceptualize risk. Future work incorporating multimodal brain-based risk and resiliency markers simultaneously is necessary to continue to develop our ability to embrace the complexity and considerable promise in this area. To this end, well-powered studies and large-scale consortia, such as Computerized Assessment for Psychosis Risk (CAPER) and Multisite Assessment of Psychosis Risk (MAP), should carefully consider these issues when rising to meet this need.

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