Review

Biological Psychiatry: GOS

Neuropsychology and Neurobiology of Negative Schizotypy: A Selective Review

Ling-ling Wang, Simon S.Y. Lui, and Raymond C.K. Chan

ABSTRACT

Schizotypy refers to a latent personality organization that reflects liability to schizophrenia. Because schizotypy is a multidimensional construct, people with schizotypy vary in behavioral and neurobiological features. In this article, we selectively review the neuropsychological and neurobiological profiles of people with schizotypy, with a focus on negative schizotypy. Empirical evidence is presented for alterations of neuropsychological performance in negative schizotypy. We also cover the Research Domain Criteria domains of positive valence, social process, and sensorimotor systems. Moreover, we systematically summarize the neurobiological correlates of negative schizotypy at the structural, resting-state, and task-based neural levels, as well as the neurochemical level. The convergence and inconsistency of the evidence are critically reviewed. Regarding theoretical and clinical implications, we argue that negative schizotypy represents a useful organizational framework for studying neuropsychology and neurobiology across different psychiatric disorders.

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PERSPECTIVES

The Conceptualization of Schizotypy

Following Rado who coined the term schizotype (i.e., a genetically driven schizophrenic phenotype) (1), Meehl proposed that schizotaxia refers to inherited neural defects that result from an individual's genetic vulnerability to schizophrenia, while schizotypy refers to a personality organization that reflects a liability to schizophrenia as a result of both genetic (i.e., schizotaxia) and environmental factors (2). Although it has not been well incorporated into the current diagnostic classification systems in psychiatry, schizotypy can manifest as clinical entities such as schizotypal or schizoid personality disorder. Moreover, schizotypy can manifest as subtle, subclinical, psychotic-like phenomenology (e.g., perceptual aberrations and magical ideation) (3). Although schizotypy may not necessarily evolve into schizophrenia, people with schizotypy exhibit aberrant neuropsychological and neurobiological functioning. The schizotypy framework has been influential and represented an early attempt to study schizophrenia-related features and risks beyond traditional clinical samples of schizophrenia (2). It also extended research to high-risk populations and appears to have contributed to the subsequent development of constructs such as clinical high risk for psychosis (CHR), ultra-high risk (UHR), and at-risk mental state (ARMS) (4).

The proposition that clinical (schizophrenia) and subclinical (schizotypal) features may originate from the same neurobiological processes (2,5) provides strong support for schizotypy as a useful organizational framework for studying the etiology of schizophrenia, because subclinical populations are unlikely to be affected by certain potential confounds, such as antipsychotic medications, disease chronicity, and long-term hospitalization (6).

The role of resilience factors that minimize the risk of psychosis conversion in people with schizotypy may unveil protective and compensatory neurobiological processes, which may provide useful insights related to possible prevention of psychosis development. In fact, unlike the CHR, UHR, and ARMS constructs, which are believed to lie nearer to the clinical extreme on the schizophrenia spectrum, schizotypy represents a milder, subclinical condition (or even preclinical condition for people with "happy schizotype") (see Supplemental Introduction 1.1), with high variability in the risk of psychosis conversion. Importantly, it is believed that the risk and resilience factors dynamically influence the risk of future conversion to schizophrenia in people with schizotypy (7). In fact, earlier research on CHR, UHR, and ARMS revealed a substantial risk of conversion to psychosis (up to 40%) (8,9), higher than that found in people with schizotypy (10).

Moreover, schizotypy shows higher phenotypic heterogeneity. Whereas the UHR and ARMS are defined primarily based on attenuated/transient positive symptoms (4), the conceptualization of the CHR includes genetic risk and deterioration syndrome, which refers to an individual who has met the diagnostic criteria for schizotypal personality disorder or has a first-degree relative with a psychotic disorder and who has shown marked deterioration in functioning over the past year (11). Unlike CHR, UHR, and ARMS, schizotypy encompasses 3 different dimensions, including positive, negative, and disorganized dimensions (12), which generally correspond to the positive symptoms, negative symptoms, and disorganized symptoms in patients with schizophrenia, respectively (13).

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Transdiagnostic Applications of the Schizotypy Framework

The transdiagnostic approach posits that our current diagnostic classification systems may not identify valid, biologically distinct phenotypes (14). Therefore, it is necessary to study the shared and distinct psychopathologies and neurobiological features across different clinical populations (15,16). The Research Domain Criteria (RDoC) (15) and the Hierarchical Taxonomy of Psychopathology (16) are notable examples of advocating the transdiagnostic approach (see Supplemental Introduction 1.2).

Although the schizotypy construct was originally designed to study schizophrenia and related psychosis (2), recent research has begun to adopt a broader, transdiagnostic approach to schizotypy. Specifically, schizotypal features, such as anhedonia, have been studied in many other disorders, such as major depressive disorder (10,17), personality disorders (18), and attention-deficit/hyperactivity disorder (19). This line of research is important to understanding the complex interactions between psychiatric comorbidity traits and patients' behavior, cognitions, and brain functions (see Supplemental Introduction 1.3).

The transdiagnostic approach may be valuable in accounting for the pluripotency of schizotypy, i.e., the phenomenon wherein schizotypy can evolve into different psychiatric disorders. For example, people with schizotypy have shown higher incidence rates of major depressive disorder than their counterparts without schizotypy (20). Given that schizotypy is a heterogeneous phenotype, different dimensions of schizotypy may have different levels of risk of conversion to different psychiatric disorders (see Supplemental Introduction 1.4). Moreover, given that schizotypal traits have substantial impact on affective and social functioning (21), the transdiagnostic approach to studying schizotypy (especially negative schizotypy) in different psychiatric disorders can be a useful framework for tackling the challenge of phenotypic heterogeneity in psychiatry (22) (see Supplemental Introduction 1.5).

Negative Schizotypy

Schizotypy comprises positive, negative, and disorganized dimensions (6) (see Supplemental Introduction 1.6). Among the 3 dimensions, the negative schizotypy dimension is the core risk factor for schizophrenia (23). Genetic studies with population-based samples of adolescents who exhibited psychotic-like experiences (i.e., the positive schizotypy dimension) failed to provide evidence to support any overlapping genetic architecture between positive schizotypy and schizophrenia (24), suggesting that the biological proximity between the 2 entities may be low. In contrast, a previous family study showed that positive and negative symptoms in patients with nonaffective psychosis predicted positive and negative schizotypy in their nonpsychotic relatives, respectively (23). Furthermore, many other studies have supported the familiality of the negative schizotypy dimension in patients with schizophrenia (25–30) and people with schizotypy (31,32).

Previous studies have consistently shown that negative schizotypy predicted the occurrence of UHR and schizophrenia (33–37), and its implications have been emphasized in several recent reviews (38,39). Although negative symptoms have long been considered to be traits rather than states, Chan *et al.* (38) proposed that trait-like and state-like properties can coexist in negative symptoms such that people at risk of developing psychosis exhibited negative symptoms long before psychosis onset (37,40) and only showed rapid negative symptom elevation shortly before psychosis onset (34). As such, negative symptoms may exhibit trait with state elevation properties (38). Negative schizotypy can be ascertained by various methods (see Supplemental Introduction 1.6). In this article, we summarize the current evidence for neuropsychological and neurobiological features of negative schizotypy. We selectively focused on 3 important domains, namely 1) the positive valence system, 2) the social process system, and 3) the sensorimotor system, according to the newly revised RDoC initiative (41). Given that the neuropsychology and neurobiology of these domains have been relatively understudied, and the study designs and measures varied considerably across studies, we did not adhere to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, and it is unlikely that our article search was exhaustive or complete.

SUMMARY OF EMPIRICAL EVIDENCE

Neuropsychology of Negative Schizotypy

Ettinger *et al.* (42) selectively reviewed deficits in attention, inhibitory control, working memory, and other types of memory in people with schizotypy, and Steffens *et al.* (43) conducted a meta-analysis on cognitive inhibition deficits in people with schizotypy. Cohen *et al.* (22) selectively reviewed social and affective neuropsychological deficits in people with schizotypy. Moreover, Lenzenweger (44) provided a qualitative review of findings of experimental psychology in schizotypy. Giakoumaki conducted a qualitative review of cognitive and prepulse inhibition deficits in schizotypy (45). These authors concluded that people with schizotypy exhibited neuropsychological/cognitive impairments that resembled those seen in patients with schizophrenia, although to a milder extent (22,42–45).

Since publication of the reviews mentioned above (22,42–45), the number of studies on the neuropsychology of negative schizotypy has been growing. These studies have utilized behavioral paradigms to tap into neurocognition, social cognition, and reward processing to elucidate putative mechanisms of negative schizotypy. Moreover, advancing neuroimaging technology has allowed researchers to apply multimodal investigations to identify neurobiological mechanisms of negative schizotypy (46). In this article, we focused on 3 important neuropsychological domains, namely 1) the positive valence system, 2) the social process system, and 3) the sensorimotor system. The positive valence system is responsible for behavioral responses to motivational situations and contexts, such as reward seeking, consummatory behavior, and reinforcement learning, while the sensorimotor system concerns the control, execution, and refinement of motor actions. Lastly, the social process system mediates behavioral responses to interpersonal and social settings (such as perception and interpretation of others' actions) and is closely related to social functioning (41,47).

Regarding the positive valence domain, previous studies have utilized an effort-based decision-making task (48). The results have shown that people with negative schizotypy are impaired in the ability to modulate motivated behavior to adapt to changing environments (i.e., reward magnitude and probability) (49–51). Moreover, they showed reduced positive affect in response to positive stimuli, including pictures and film clips (52,53). One study (54) utilized the Anticipatory and Consummatory Pleasure task (55) to assess the positive valence domain and reported that, compared with control participants, people with negative schizotypy showed altered affective experiences after viewing slides of different valences and a failure to translate emotion into motivated behavior, a phenomenon called emotion-behavior decoupling (54). However, another study that used the Anticipatory and Consummatory Pleasure task with people with schizotypy did not replicate those findings, perhaps due to the divergent methods used to define negative schizotypy (56). In short, previous evidence supported the idea that negative schizotypy is associated with an altered positive valence system.

Regarding the social process system, previous studies showed that people with negative schizotypy rated sad and neutral faces more negatively than control participants (57). Additionally, the severity of negative schizotypy traits was negatively correlated with the accuracy of facial emotion recognition (58–60). Moreover, they were more impaired in empathy than people with other schizotypy dimensions and control participants (61). Furthermore, the evidence further suggested that empathy served as a mediator that linked negative schizotypy with social functioning (61,62). A recent meta-analysis concluded that theory of mind (ToM) impairment is correlated with both the positive and negative dimensions of schizotypy but not with the disorganized dimension (63). Notably, the patterns of association between ToM and schizotypal dimensions appeared to differ from that found in patients with schizophrenia, i.e., ToM impairment was strongly correlated with the disorganized dimension of schizophrenic psychopathologies (64). Taken together, previous evidence apparently suggested that negative schizotypy is associated with impairments in both basic and higher-level social processes.

Regarding the sensorimotor system, previous studies have reported an intermediate level of neurological soft signs (NSSs) in people with schizotypy, higher than control participants but lower than patients with schizophrenia (65). NSSs are non-localizable neurological abnormalities that affect sensory integration, motor coordination, and motor sequencing and reflect underlying disrupted neural circuitries in the cortical and subcortical regions (66). Negative schizotypy, but not positive schizotypy, is associated with increased NSSs during motor coordination and motor sequencing tasks (65). Moreover, one study found that people with negative schizotypy showed more NSSs than their counterparts with positive schizotypy and control participants (67). A longitudinal study measured schizotypal features (at baseline and 2 years) and NSSs (at 2 years) in 169 male conscripts and found that the prevalence of NSSs at 2 years was significantly correlated with negative schizotypy at baseline and at 2 years, thereby supporting the consistency of this association over time (68). However, most of the studies mentioned above were limited by small sample sizes and a lack of replication samples.

Neurobiology of Negative Schizotypy

Advances in neurosciences have allowed deeper investigations into how psychological processes arise from neurobiological mechanisms (69). We reviewed studies using various neuroimaging designs, including magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS) because multiple modalities of investigation can better clarify the neurobiological mechanisms of negative schizotypy (46). Despite an increase in neuroimaging research on people with schizotypy, the current evidence remains inconsistent. Tonini *et al.* (70) systematically reviewed 84 studies that measured the association between brain structure, brain activation, and resting-state brain connectivity and schizotypy in both nonclinical and clinical cohorts. The authors failed to quantitatively identify any consistent morphological or functional characteristics for schizotypy (70).

Structural MRI Findings. Tonini *et al.*'s systematic review of structural MRI studies showed that negative schizotypy was associated with gray matter changes in subcortical regions and regions that belong to the default mode, visual, limbic, somatomotor, frontoparietal, and ventral attention networks (70). Among people with negative schizotypy, the severity of negative schizotypy traits was positively correlated with the thickness of the right temporoparietal junction (TPJ), i.e., the putative neural substrate for ToM processing (71). A recent study utilized a sample of 110 adolescents to examine the longitudinal association between negative schizotypy trait severity and brain structural changes; higher negative schizotypal traits were associated with a smaller increase in the volume of the bilateral pallidum over time and reduced volume of the thalamus over the entire age range (72). The pallidum and thalamus are core regions for processing reward and emotion (73,74), and the thalamus has been implicated in NSSs of patients with schizophrenia (75). However, the relationships between the severity of negative schizotypy, tractography, and gray matter volume of the brain remain unclear.

Functional MRI Findings. Altered functional connectivity may lead to abnormal functional integration, inference, and learning, which can then evolve into schizophrenic symptoms (76). Several studies have investigated the associations between resting-state functional connectivity and negative schizotypy; however, the previous results remained inconsistent (70). Preliminary evidence suggested that the severity of negative schizotypy was correlated with altered functional connectivity in the default mode, frontoparietal, ventral attention, visual, and somatomotor networks (70). Corticostriatal connectivity is central to the neuropathology of schizophrenia (77), and the striatum is the key brain region involved. Previous findings have also suggested that people with negative schizotypy showed both hyper- and hypocorticostriatal connectivity (78,79). Moreover, a recent longitudinal study found that reduction in corticostriatal connectivity was correlated with behavioral improvements in the positive rather than the negative schizotypy dimension (80). Taken together, these findings suggest that the underlying neural mechanisms for negative schizotypy may be less likely to vary over time (81).

Task-based functional MRI (fMRI) studies of people with negative schizotypy have yielded divergent findings (70). One

important shortcoming of task-based fMRI studies is related to the different tasks used, which has resulted in vast heterogeneity of task designs. For task-based fMRI studies that utilized reward-processing tasks (i.e., the positive valence system), the results showed that people with negative schizotypy exhibited decreased activation in the ventral lateral prefrontal cortex, medial prefrontal cortex, and rostral anterior cingulate cortex (ACC) while evaluating positive stimuli (82,83). For task-based fMRI studies that utilized monetary-incentive delay tasks, the results showed that people with negative schizotypy exhibited reduced activation in the amygdala and putamen during reward consummation but reduced striatum activation during reward anticipation (84). For the social process system, people with negative schizotypy exhibited reduced activation in the frontoparietal regions and the amygdala during facial emotional processing (70). One study examined facial emotion processing in people with negative schizotypy and found that they showed reduced amygdala activation during fearful and neutral face conditions (85). They also exhibited reduced amygdala–medial prefrontal cortex/dorsal ACC functional connectivity during the happy and fearful face conditions. Another study (86) examined the association between negative schizotypy and brain activity during ToM and empathy tasks and reported a positive relationship between negative schizotypy and greater activation in the TPJ, suggesting possible compensatory neural mechanisms. To our knowledge, no previous study has utilized task-based fMRI to investigate the neural correlates of NSSs (i.e., the sensorimotor domain) in people with negative schizotypy. Taken together, previous studies have suggested that negative schizotypy is associated with altered neural activation during operation of the positive valence and social process systems. However, future large-scale replication studies are needed to verify these preliminary findings.

MRS Findings. Excitatory (glutamate [Glu]) and inhibitory GABA (gamma-aminobutyric acid) neurotransmitter functions are important in the development of schizophrenia (87). To date, only a few studies have examined Glu, GABA, and related neurometabolites using MRS in people with negative schizotypy and reported that they had Glu, GABA, and Glu/GABA levels comparable to those of control participants (88–90). These 2 neurotransmitters appeared to exert different effects on neurocognitive performance in the 2 groups (89). There was a negative correlation between Glu levels and cognitive ToM performance in people with negative schizotypy, but no such correlation was found in control participants (89). The Glu level in the ACC was negatively correlated with striatal activation in response to emotion stimuli in negative schizotypy (91). Moreover, the excitatory/inhibitory (E/I) balance (Glu/GABA ratio) was negatively correlated with social functioning in people with negative schizotypy, but no such correlation was found in control participants (90). Glu level in the ACC was negatively correlated with gray matter volume in the ACC of people with positive schizotypy (92). In contrast, lower prefrontal GABA and Glu levels were found in people with high total schizotypy scores (93). Therefore, dysfunctions in the Glu and GABA system may not be specific to people with negative schizotypy, who also show heterogeneity in Glu and GABA levels. Taken together, the evidence has suggested that Glu and GABA levels are unaltered in people with negative schizotypy, but the effects of these neurotransmitter on neurocognitive performance in negative schizotypy differ from that in healthy people.

CONVERGENCE OF EVIDENCE

To integrate the schizotypy framework with the current RDoC framework, we proposed 3 important domains, i.e., the positive valence system, the social process system, and the sensorimotor system (41). In schizophrenia research, an integrated theoretical model for putative mechanisms of negative symptoms has been proposed (38) in which it is tacitly suggested that the aforementioned 3 systems may be core, interconnected domains. Given the close relationship between schizophrenia and schizotypy, we attempted to interpret the neuropsychological and neurobiological evidence for negative schizotypy in accordance with this 3-domain structure, as shown in Table 1. Despite the apparent convergence of evidence gathered at the neuropsychological and neurobiological levels, it should be interpreted with caution because preliminary findings from individual studies have not been replicated (see Table 1), and different scales have been used to ascertain negative schizotypy indifferent studies.

Regarding the positive valence system, considerable neuropsychological evidence supports the idea that negative schizotypy is associated with impaired reward processing (49–54). Likewise, neuroimaging evidence supports the proposition that negative schizotypy is associated with alterations in brain regions responsible for reward processing (72,78,79,82–84).

Regarding the social process system, neuropsychological evidence supports the existence of social cognitive impairments in people with negative schizotypy, which affect their facial emotion processing (57–60), empathy (61), and ToM (63). However, it appears that the neuroimaging evidence and neuropsychological evidence for negative schizotypy are difficult to reconcile. First, fMRI evidence suggests that negative schizotypy is associated with stronger activation of the TPJ (86) during social cognition tasks. Second, structural MRI evidence suggests that higher negative schizotypy dimension is correlated with greater TPJ thickness (71). Given that the TPJ region is responsible for social cognitive processing (94), previous findings (71,86) regarding the TPJ appear counterintuitive or may represent compensatory neurobiological alterations for behavioral deficits in social cognition. Lastly, MRS evidence regarding Glu and GABA levels in people with negative schizotypy remains limited, but preliminary results have indicated comparable Glu and GABA levels in the ACC in people with negative schizotypy and control participants (88–90). Given that previous MRS studies could not simultaneously measure Glu and GABA levels in multiple brain regions, it remains unclear whether the comparable Glu and GABA levels in people with negative schizotypy and control participants (88–90) involve the whole brain or merely the ACC.

Regarding the sensorimotor system, neuropsychological evidence supports that people with negative schizotypy have more NSSs than their counterparts with schizotypy (65,67,68). The structural MRI and fMRI evidence also suggest that the

Table 1. Summary of the Neuropsychological and Neurobiological Findings From the Positive Valence, Social Process, and Sensorimotor Systems in Negative Schizotypy

		Neurobiology			
	Neuropsychology	Structural MRI	Resting-State fMRI	Task-Based fMRI	MRS
Positive Valence System	Impairment in modulating motivation for reward (50,51)[a] (49)[b] Reduced pleasure experience from positive stimuli (52,53)[a] Impairment in translating emotion into motivation (54)[a]	Reduced increase of bilateral pallidum volumes positively correlated with negative schizotypy (72)[c]	Hyper- and hypo corticostriatal connectivity (78,79)[c]	Reduced vlPFC, mPFC, and rostral ACC activation to positive stimuli (82)[d] (83)[a] Reduced amygdala and putamen activation during reward consummation (84)[c] Reduced striatum activation during reward anticipation (84)[c]	Glu levels negatively correlated with striatal activation to emotion stimuli of negative schizotypy (91)[e]
Social Process System	Ratings of sad faces negatively correlated with negative schizotypy (57)[a] Facial emotion recognition negatively correlated with negative schizotypy (58)[c] (59,60)[g] Impairment in empathy (61)[a] Impairment in ToM (63)[i]	Right TPJ thickness positively correlated with negative schizotypy (71)[c]	Default mode network connectivity correlated with negative schizotypy (70)[f]	Reduced frontoparietal and amygdala activation during facial emotional processing (70)[f] TPJ activation positively correlated with negative schizotypy (86)[h]	Glu levels negatively correlated with cognitive ToM of negative schizotypy (89)[a]
Sensorimotor System	Stable and increased NSSs (65,67)[h] (68)[c]	Reduced thalamus volumes positively correlated with negative schizotypy (72)[c]	Somatomotor network connectivity correlated with negative schizotypy (70)[f]	No previous study was found	Glu/GABA ratio negatively correlated with social functioning of negative schizotypy (90)[a]

The majority of the contents in the table were gathered based on individual studies in the literature; review and meta-analytic papers are noted.

ACC, anterior cingulate cortex; fMRI, functional magnetic resonance imaging; GABA, gamma-aminobutyric acid; Glu, glutamate; IFG, inferior frontal gyrus; mPFC, medial prefrontal cortex; MRS, magnetic resonance spectroscopy; NSSs, neurologic soft signs; ToM, Theory of Mind; TPJ, temporoparietal junction; vlPFC, ventral lateral prefrontal cortex.

[a]The Chapman Scale for Social Anhedonia.

[b]The 17-item Social Anhedonia Scale-Brief.

[c]The Schizotypal Personality Questionnaire.

[d]The Revised Physical Anhedonia Scale.

[e]The Oxford and Liverpool Inventory of Feelings and Experiences Scale.

[f]Review papers.

[g]The Schizotypal Personality Questionnaire-Brief Revised.

[h]The Revised Social Anhedonia and Physical Anhedonia Scales.

[i]Meta-analytic papers.

thalamus and the sensorimotor network are altered in people with negative schizotypy (70,72). However, the paucity of task-based fMRI coupled with NSS tasks is an issue and should be addressed in future research.

IMPLICATIONS AND FUTURE RESEARCH DIRECTIONS

Negative schizotypy may reflect the early emergence of negative symptoms in nonclinical populations. In fact, following the staging model of psychosis (95), schizotypy can be regarded as a relatively more preclinical condition than CHR, UHR, and ARMS because the latter conditions are associated with higher conversion risk to schizophrenia (8,9). Instead, schizotypy has pluripotent properties (7), and its evolution is far from deterministic because resilience and protective factors may prevent the future occurrence of psychiatric disorders (96). As a result, schizotypy provides a valuable opportunity for preventive medicine in psychiatry. This issue is particularly important for people with negative schizotypy because firmly established negative symptoms in patients with schizophrenia are usually resistant to treatment (97). The Prodromal Inventory of Negative Symptoms has recently been developed to capture subtle negative symptoms in subclinical populations (98) and can supplement schizotypy scales to identify people with negative schizotypy.

Apart from its clinical implications, the negative schizotypy dimension has great advantages related to advancing etiological research in schizophrenia. Compared with other schizotypy dimensions, negative schizotypy shows a relatively stable trajectory and may better reflect the underlying neurodevelopmental alterations for liability to schizophrenia (7). We advocate transdiagnostic application of the negative schizotypy framework to unveil the pluripotency of this construct. Furthermore, we advocate the inclusion of individuals with negative schizotypy, positive schizotypy, CHR/UHR/ARMS,

first-episode, and multiple-episode schizophrenia as participants and believe that such an extended psychosis staging model will offer an informative account of the neurodevelopmental evolution of schizophrenia.

The 3 RDoC domains of positive valence, social process, and sensorimotor systems are important areas for future research in negative schizotypy. Although most previous studies only investigated one of these domains, a recent attempt to examine more systems at one time in people with negative schizotypy showed interesting results (99), where anticipation of monetary reward was correlated with cognitive empathy, while anticipation of social reward was associated with affective empathy. Previous evidence from patients with schizophrenia also suggested that NSSs are correlated with social cognition (100,101). Future research should explore how these 3 domains/systems may interact with each other to influence the risk of psychosis conversion as well as symptom manifestation in people with negative schizotypy. Unveiling the possible hierarchical relationship between these 3 domains may better inform the development of interventions.

Multimodal strategies that combine multiple neurobiological measures such as MRS and MRI scanning are preferred for several reasons (102). First, from a computational perspective, higher-level behavioral deficits are rooted in lower-level biological abnormalities. Thus, parsing the intermingled mechanisms into different independent hierarchical levels may not be the most suitable approach. Instead, multimodal studies can directly and simultaneously measure the operations of psychiatric phenomena at different levels. For example, the imbalance of E/I signals is believed to contribute to negative symptoms, but the exact pathway of neurochemical dysregulation to negative symptoms remains unclear. A recent multimodal fMRI and MRS study (90) found that E/I balance was correlated with reward value adaptation, mediated by resting-state functional connectivity. In addition, E/I balance was negatively correlated with social anhedonia in the general population and with social functioning in people with negative schizotypy. Others have used multimodal neuroimaging techniques to examine the relationship between hippocampal regional cerebral blood flow and striatal dopamine synthesis capacity, as well as the relationship between Glu levels and corticolimbic response to emotion in people with UHR and schizotypy (91,103). Future research should apply multimodal strategies to identify coherent neuropathological pathways in people with negative schizotypy.

Another useful strategy is to complement the correlation results using machine learning classification, which determines whether measurements can effectively categorize participants at risk. For instance, Krohne *et al.* (104) reported that the features extracted from functional networks during a social cognition task and supervised machine learning can be used to categorize participants into subgroups with different degrees of social anhedonia.

Future research should also refine the sampling methods used to study negative schizotypy. Previous studies of schizotypy have mainly recruited college students, who have already reached adulthood (7). However, evidence suggested that schizotypy features can manifest early in childhood, and childhood schizotypy can predict the future development of psychiatric disorders during adolescence (105). Epidemiological studies have indicated that the prevalence of subclinical psychotic symptoms during late childhood and adolescence is higher than that in adulthood (106). Childhood and adolescence are vulnerable periods, and abnormal neurodevelopment during these early periods may precede schizophrenia onset (107). Research on negative schizotypy should be extended to childhood and early adolescence and investigate how early-life events such as childhood trauma could shape schizotypy dimensions and psychotic experiences (108,109).

Likewise, variations in fMRI behavioral tasks and imaging protocols should be considered. For example, the translation of MRS to research has been strongly impeded by a lack of technical standardization, although a few guidelines for data acquisition and reporting of MRS have been issued (110). The RDoC working group (47) has also made clear recommendations regarding the suitable neuropsychological tasks for each of the RDoC constructs (111). Better standardization of instruments and tasks and scanning protocols can improve comparability and replicability across studies.

CONCLUSIONS

This article focused largely on the positive valence, social process, and sensorimotor systems in negative schizotypy. Despite our limited focus and selective inclusion of articles, our findings provide insightful perspectives for future research on schizotypy. Negative schizotypy is associated with neuropsychological and neurobiological abnormalities and can facilitate the investigation of risk and resilience factors, as well as compensatory mechanisms for the development of schizophrenia and other psychiatric disorders. Transdiagnostic applications of the schizotypy framework will refine the psychosis staging model. The positive valence, social process, and sensorimotor systems are particularly relevant to negative schizotypy. Future research should apply multimodal neuroimaging techniques, standardized imaging protocols, and suitable neuropsychological tasks.

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ARTICLE INFORMATION

From the School of Psychology, Shanghai Normal University, Shanghai, China (L-LW); Department of Psychiatry, School of Clinical Medicine, The University of Hong Kong, Hong Kong Special Administrative Region, China (SSYL); Neuropsychology and Applied Cognitive Neuroscience Laboratory, CAS Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences, Beijing, China (RCKC); and the Department of Psychology, University of Chinese Academy of Sciences, Beijing, China (RCKC).

L-LW and SSYL contributed equally to this work.

Address correspondence to Raymond C.K. Chan, Ph.D., at rckchan@psych.ac.cn.

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