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Psychomotor slowing in Schizophrenia: Implications for endophenotype and biomarker development

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ABSTRACT

Motor abnormalities (e.g., dyskinesia, psychomotor slowing, neurological soft signs) are core features of schizophrenia that occur independent of drug treatment and are associated with the genetic vulnerability and pathophysiology for the illness. Among this list, psychomotor slowing in particular is one of the most consistently observed and robust findings in the field. Critically, psychomotor slowing may serve as a uniquely promising endophenotype and/or biomarker for schizophrenia considering it is frequently observed in those with genetic vulnerability for the illness, predicts transition in subjects at high-risk for the disorder, and is associated with symptoms and recovery in patients. The purpose of the present review is to provide an overview of the history of psychomotor slowing in psychosis, discuss its possible neural underpinnings, and review the current literature supporting slowing as a putative endophenotype and/or biomarker for the illness. This review summarizes substantial evidence from a diverse array of methodologies and research designs that supports the notion that psychomotor slowing not only reflects genetic vulnerability, but is also sensitive to disease processes and the pathophysiology of the illness. Furthermore, there are unique deficits across the cognitive (prefix "psycho") and motor execution (root word "motor") aspects of slowing, with cognitive processes such as planning and response selection being particularly affected. These findings suggest that psychomotor slowing may serve as a promising endophenotype and biomarker for schizophrenia that may prove useful for identifying individuals at greatest risk and tracking the course of the illness and recovery.

The current understanding of the trajectory and pathophysiology of schizophrenia spectrum disorders has advanced considerably. However, attempts to improve early identification and prevention in at-risk populations, and to predict treatment response and clinical outcomes in schizophrenia remain promising but limited [1,2]. This has led to efforts to identify endophenotypes that reflect the genetic risk for the illness, as well as biomarkers sensitive to disease progression and treatment response [3]. Endophenotypes are a specific type of biomarker that reflect abnormal biochemical, neurophysiological, neuroanatomical, cognitive, and neuropsychological characteristics associated with the genetic vulnerability for an illness that must also be state-independent and present within affected families at a higher rate than in the general population [4]. In contrast, a biomarker for schizophrenia is any objectively measured characteristic that is an indicator of the risk for or presence of the disorder [3,5]. Broadly, biomarkers are intended to ultimately provide a means for identifying individuals at greatest risk for an illness, as well as track progression and remission. Consistent with a diathesis-stress model of psychosis, endophenotypes reflect the inherent diathesis whereas biomarkers are sensitive to a myriad of stressors and pathophysiological processes that contribute to the onset of the disorder.

Accumulating evidence indicates that motor dysfunction commonly observed in psychosis is associated with genetic vulnerability for the disorder, the severity and progression of the illness, as well as structural and functional abnormalities in motor circuitry across the different stages of psychosis [6–16]. As this abnormal motor circuitry overlaps with neural regions implicated in prominent etiological models of schizophrenia [17,18], indices of motor dysfunction may serve as promising endophenotype and biomarker candidates in psychosis. In addition, motor dysfunction occurs in the absence and presence of antipsychotic medication [19], indicating that motor abnormalities cannot be accounted for by antipsychotic medication alone.

One motor deficit in particular, psychomotor slowing, has been called "the closest thing to a North-star in schizophrenia research" [20]. Psychomotor slowing is an observable and measurable reduction in the

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initiation, amount, or speed of movement that results from deficits in either the automatic and controlled cognitive processes involved in movement (i.e., the prefix "psycho"), or the direct execution of movement itself (i.e., the root word motor). It can be measured in several ways such as traditional processing and motor speed measures (e.g., Trails Making Test, Digit Symbol Substitution Test, finger tapping), reaction time paradigms, actigraphy, and clinician rated slowing. This slowing of action planning and execution co-occurs with other motor symptoms in psychosis such as spontaneous involuntary movements (e.g., dyskinesias) [21,22], and is a core feature of the disorder that is present across the different stages of schizophrenia (i.e., risk populations, first-episode, chronic) [23–25]. However, it is currently unclear if psychomotor slowing in psychosis primarily reflects the disorder's genetic vulnerability (i.e., endophenotype) or broader disease processes (i.e., biomarker) more specifically. Thus, considering the current evidence on psychomotor slowing as it relates to genotype-phenotype pathways, pathophysiology, staging of the disorder, and response to treatment will inform both the development of motor-related biomarkers for psychosis and diathesis-stress models of psychosis more broadly.

The purpose of this review is to provide a summary of the current findings on psychomotor slowing in schizophrenia. We first introduce the conceptual history of psychomotor slowing before discussing the cognitive and motor processes implicated in slowing. Then we review the putative neural underpinnings of psychomotor slowing in schizophrenia before pivoting to a review of the current evidence for psychomotor slowing in schizophrenia, and evidence suggesting it reflects the genetic vulnerability for the disorder (i.e., endophenotypes) and disease mechanisms (i.e., biomarkers).

1. An introduction to psychomotor slowing in Schizophrenia

1.1. History of psychomotor slowing in schizophrenia

Portending modern biomarker work, psychomotor slowing has been considered an important behavioral manifestation of the pathophysiology of psychosis since the earliest phenomenological descriptions of the illness. For example, in 1874, Kahlbaum described various hypokinetic motor signs (slowed and decreased movements) in catatonia, their link to volition and motivation, and suspected abnormal neural activity within the cerebral motor system [26]. Similarly, in his book on psychomotor symptoms, Kleist specifically suspected motor slowing to arise from a " . . . dissociation between the cerebellar-frontal-system and the sensorimotor system of the central gyri (i.e. primary motor cortex)" [27, p. 147]. Roughly thirty years later, Wernicke introduced the term "psychomotor", and classified psychomotor slowing as akinetic (reduced movements) and hypothesized that dysconnectivity between neural regions gives rise to akinesias (slowed or lack of movement) observed in psychosis [28–31]. Furthermore, he separated intrapsychic akinesia (lack of intrinsic motivation/initiative, which affects the whole motor system and compromises self-initiated movements much more than reactive movements) from psychomotor akinesia (negativism, flexibilitas cerea, rigor, and gegenhalten). Therefore, Wernicke considered non-intentional movements without outcome expectations to be psychomotor slowing, which is in contrast to Kraepelin who used the term psychomotor slowing to describe volitional movements as well [27]. Further, whereas Wernicke believed that psychomotor slowing was important for the broader concept of psychosis, Kraepelin (and Bleuler) firmly integrated psychomotor slowing into their clinical conceptualization of schizophrenia (rather than psychotic disorders more broadly). For example, Bleuler observed that "spontaneous movements are . . . executed slowly and weakly" and even ambulatory and active patients with schizophrenia do so "slowly, tremulously, and feebly" [32].

Early twentieth century experimental findings in patients with schizophrenia paralleled early clinical descriptions of psychomotor slowing, pointing to slowed responses across a wide range of task paradigms and sensory modalities [33–36]. Indeed, a great deal of early and mid 20th century work sought to determine the possible cognitive contributions to task-related slowing in patients with schizophrenia (see [34]), as well as the utility of slowing for predicting prognosis, symptomatology, and discriminating amongst patient subgroups and other disorders (e.g., depression) [20,37,38]. With the advent of prominent information processing models [39,40], explanations for task-related slowing progressed from non-specific attentional deficits and clinical characteristics (e.g., motivation, cooperation, apathy) [41–43] to also include sensory filtering and short term memory abnormalities [44,45] and slowed motor execution [37,46]. This focus on determining the subprocesses that contribute to psychomotor slowing has persisted as a dominant area of research in schizophrenia (see [47]) with much recent work attempting to identify the specific neural substrates of slowing in psychosis [48–53].

1.2. Psychomotor slowing within the broader psychomotor syndrome of schizophrenia

Psychomotor slowing exists as a symptom within a broader psychomotor syndrome exhibited in schizophrenia. Other psychomotor symptoms include neurological soft signs, catatonia, and extrapyramidal signs. Neurological soft signs (NSS) are subtle deficits in fine motor coordination, sensory integration, and sequencing of motor actions. Catatonia reflects a cluster of symptoms such as stupor, motor agitation, posturing, and negativism. Extrapyramidal signs include dyskinesias, parkinsonism (e.g., tremor, rigidity, bradykinesia), and dystonia. It is notable that there is considerable overlap across the above-mentioned symptoms that comprise the psychomotor syndrome and often co-occur within an individual [19,22]. Due to this overlap, it is difficult to determine the primary nature of motor slowing given its vast overlap with negative symptoms (avolition), catatonia, and extrapyramidal signs [21,54,55], all of which include psychomotor slowing as a characteristic feature of their symptom cluster. This is a particular issue when determining the nature of slowing in self-initiated movements given symptoms such as abulia and apathy are common in psychosis and would themselves result in reduced movement.

Furthermore, consistent with Rogers [56] "conflict of paradigms", it is difficult to determine if psychomotor slowing across these different symptom clusters reflects real etiological differences or are due to various investigators attributing the same clinical phenomenon to different etiologies. Because of this, several definitions of psychomotor slowing have emerged that place differing etiological emphasis including volition and deficits in information processing [57]. Although there is evidence for each of these models for understanding psychomotor dysfunction, the present review focuses on outward and measurable manifestations of psychomotor slowing, as they are clinically feasible and amenable to endophenotype and biomarker applications. However, it is important to acknowledge that the definition of psychomotor slowing used in the current review is quite broad in that it encompasses a large number of cognitive and motor processes. This broad definition was used in order to accurately reflect the complexity of the various potential underlying subprocesses that may contribute to slowing in psychosis.

1.3. Cognitive and motor processes of psychomotor slowing

Here, the cognitive and motor sub-processes that comprise psychomotor slowing in schizophrenia are differentiated in order to better elucidate distinct deficits contributing to slowing in schizophrenia. Various automatic and controlled cognitive processes are required to translate perceived sensory information into task-related or volitional (self-initiated) responses. Visuo-motor transformations requires an initial perception of relevant stimuli, these stimuli are then held in working memory until a decision that is consistent with task demands or intended goals is reached, and then a subsequent response is made. Depending on

the complexity of the response, planning and sequencing of the movement (s) may also be required. Each of these processes is further facilitated by a number of additional cognitive and motor functions. For example, perception of stimuli requires adequate allocation of attentional resources, decision-making requires cognitive control to resolve task-relevant conflicts and plan sequences of motor actions, and execution of a response requires cognitive processes such as performance monitoring and inhibition of competing motor behaviors.

Depending on the required goal, each process may occur once, such as in a single trial of a choice reaction time paradigm or reaching for a glass, or multiple times such as in the Digit Symbol Substitution Test (DSST) or playing a piano. It is important to note that psychomotor processes involved in traditional paradigms are primarily externally triggered (i.e., those triggered by a stimulus) and are typically measured using choice reaction time paradigms or the performance of processing speed tasks (Trail Making Test [TMT]- A and B, DSST) on writing tablets. In contrast, planned and spontaneous self-initiated movements are made in the absence of a stimulus or cue and thus also involve a strong motivational and volitional component, as well as decisions regarding if and when to carry out an action [58,59], and are primarily measured via actigraphy. From this framework, the cognitive aspects of psychomotor slowing include deficits involved comparing stimuli to previously learned stimulus-response mappings in working memory (i.e., response selection), decision making, inhibiting competing responses, volition, and motor planning and sequencing. In contrast, the motor aspects of psychomotor slowing involve the relatively automatic processes involved in initiation, coordination, and execution of a response. Thus, slowing across any one or more of these sub-processes would result in the task-related slowing and slowed motor behavior observed across the schizophrenia spectrum.

Although the abovementioned cognitive and motor processes all contribute to effective movement, due to the variety of methods used to assess psychomotor slowing, coupled with the fact that the majority of research examining psychomotor slowing in psychosis is not well differentiated in regards to the sub-processes that contribute to slowing, we employ past approaches in the interest of organization [60]. Specifically, we refer to all sub-processes that occur before the initiation (i.e., onset) of movement as cognitive and the sub-processes involved in the initiation, coordination, and execution of movement as motor execution. See Table 1 for the sub-processes subsumed within these domains along with the measures that assess them. Note, the measures listed in Table 1 are not exhaustive and are meant to illustrate the types of paradigms that can be used to assess the various sub-process that may contribute to psychomotor slowing.

1.4. Neural underpinnings across the sub-processes of psychomotor processing

Regarding neural networks and circuitry, both cortico-cortical and cortico-basal ganglia networks have been proposed to subserve the cognitive and motor processes involved in visuo-motor transformations and goal-direct actions [61–63]. Critically, these same networks are well-evidenced to be altered in schizophrenia and are implicated in prominent etiological models for the illness [17,18]. Because the exact nature of how these networks and circuits functionally translate visual input to motor output is not fully understood, we largely focus on cortico-cortical networks as they relate to cognitive aspects of psychomotor behavior and cortical-striatal circuits as they relate to motor function. Although dividing these networks into distinct functional categories is primarily done to enhance conceptual clarity, it is largely consistent with a body of evidence from research in humans and non-human primates [64]. For instance, evidence from neuroimaging work with non-human primates and humans suggests that sensory information is integrated in the parietal cortex and then transformed into representations of movement-related features (e.g., intention to move, movement direction) [64–66]. Movement-related information in the parietal cortex is then projected to the premotor cortex (PMC), which is implicated in maintaining representations for potential actions and motor planning [67,68]. It has been suggested that parieto-frontal connectivity may form the fundamental space for the maintenance of potential actions that are ultimately selected by subcortical circuitry to be relayed to the primary motor cortex (M1) for execution [69,70].

1.4.1. Neural underpinnings of psychological sub-processes of psychomotor processing

Given that both attention to relevant environmental information and working memory involve parieto-frontal networks [71–74], these parieto-frontal networks may mediate the cognitive aspects of psychomotor behaviors. However, it is important to note that, depending on the required behavior, several other regions implicated in cognitive aspects of visuo-motor transformation may be involved. For instance, both the supplementary motor area (SMA) and pre-supplementary motor area (pre-SMA) contribute to planning sequences of motor behaviors [75–77]. Similarly, accurate movements require continuous monitoring of performance to ensure that any potential errors in movement are inhibited or corrected. Error monitoring is a cognitive function that relies on anterior cingulate cortex (ACC) activity. Taken together, the cognitive aspects of psychomotor behavior rely on an interconnected, multiregional network involved in processing stimuli, maintaining attention, and accurate motor planning using working memory.

Table 1
Definitions of organizational terms and sub-processes with associated measures.

Terms	Sub-Processes	Measures of Assessment
General Psychomotor Slowing		
Refers to measures of slowing that only afford a single metric of slowing in psychosis. Thus, these measures do not distinguish between the cognitive and motor sub-processes that contribute to psychomotor slowing.	Depending on the task or action performed, measures of general slowing would include most, if not all, of the cognitive and motor processes implicated in perception, decision/response selection, and motor planning and execution.	TMT- A and B; DSST; DST
Cognitive		
Refers to the cognitive sub-processes that occur prior to initiation and execution of movement, as well as the measures that assess those sub-processes.	Response Selection and Motor Planning	Traditional paradigms (e.g., DST, TMT) on writing table; reaction time paradigms; S-LRP
	Motor Inhibition	Stop Signal; Go/No-Go Task
	Volition	Actigraphy
Motor Execution		
Refers to the motor sub-processes that occur after the initiation and execution of movement, as well as the measures that assess those sub-processes.	Fine Motor Coordination	Grooved Pegboard Test
	Motor Speed	Finger Tapping; R-LRP

Note: TMT = Trail Making Test; DSST = Digit Symbol Substitution Test; DST = Digit Symbol Coding Test; S-LRP = stimulus-locked lateralized readiness potential; R-LRP = response-locked lateralized readiness potential.

1.4.2. Neural underpinnings of motor sub-processes of psychomotor processing

Ultimately, motor-related information is delivered to the primary motor cortex (M1) where it is relayed to the corticospinal tracts [64,78]. Evidence suggests that this process is subserved via cortico-basal ganglia circuitry. Specifically, the basal ganglia consist of several subcortical regions (globus pallidus, striatum, subthalamic nucleus, and substantia nigra) that are involved in two parallel, dopamine-dependent pathways critical for voluntary movement. Both pathways form closed loop circuits that originate in motor cortical neurons in the cortex (e.g., premotor and motor cortex). The direct pathway facilitates planned motor behavior via cortical projections to the striatum which then decreases the tonic inhibition of the internal segment of the globus pallidus (GPi) on thalamus, which increases thalamic projections back to the motor cortex, ultimately causing the execution of movement. In contrast, the indirect pathway suppresses movement via cortical projections to the striatum, which projects to the external segment of the globus pallidus (GPe), which projects to the subthalamic nucleus (STN), which projects to the GPi, increasing its tonic inhibition on the thalamus, which decreases thalamic projections back to the motor cortex, suppressing movement. Taken together, the motor aspects of psychomotor slowing involve the modulation of parieto-frontal networks via cortico-basal ganglia circuitry that selects from a number of cortical motor programs and projects them to M1.

1.5. Proposed pathophysiological model of psychomotor slowing in Schizophrenia

Determining the neural underpinnings of slowing in psychosis has relevance for the field's understanding of the pathophysiological mechanisms putatively contributing to development and progression of the illness. Studies utilizing task-based fMRI, resting-state functional connectivity, and fiber tracking in psychosis populations implicate altered functional activity and connectivity across the previously described neural regions and their associated psychomotor processes (see Fig. 1). For example, using fMRI, hyper- and hypoactivity and connectivity in parieto-frontal regions has been shown to be associated with psychomotor slowing in reaction time paradigms in patients [52,79,80], and has been interpreted as reflecting the cognitive aspects of slowing including response selection, decision making, cognitive control, and working memory [48–53]. Furthermore, findings from fMRI, probabilistic fiber tracking, and arterial spin labeling in patients with clinician-rated slowing (i.e., akinesia, hypokinesia, retarded catatonia) have provided evidence for abnormal functional activity and connectivity across several regions including the pre-SMA, SMA, ACC, and PMC, as well as reductions in white matter integrity from the PFC to the striatum [81–87], which further implicate deficits in performance monitoring, response inhibition, and planning in slowing.

Whereas the neural underpinnings of the cognitive components contributing to slowing have received more attention, research examining fine motor execution deficits associated with slowing is more limited. However, resting state functional connectivity between the putamen and SMA is linked to slower motor execution during fine motor tasks in patients, whereas reduced connectivity between caudate and DLPFC was linked to longer planning durations [88]. In addition, functional neuroimaging investigations of slowing in fine motor control in patients have demonstrated abnormal activity in M1, PMC, SMA, thalamus, basal ganglia, and cerebellum [89–92].

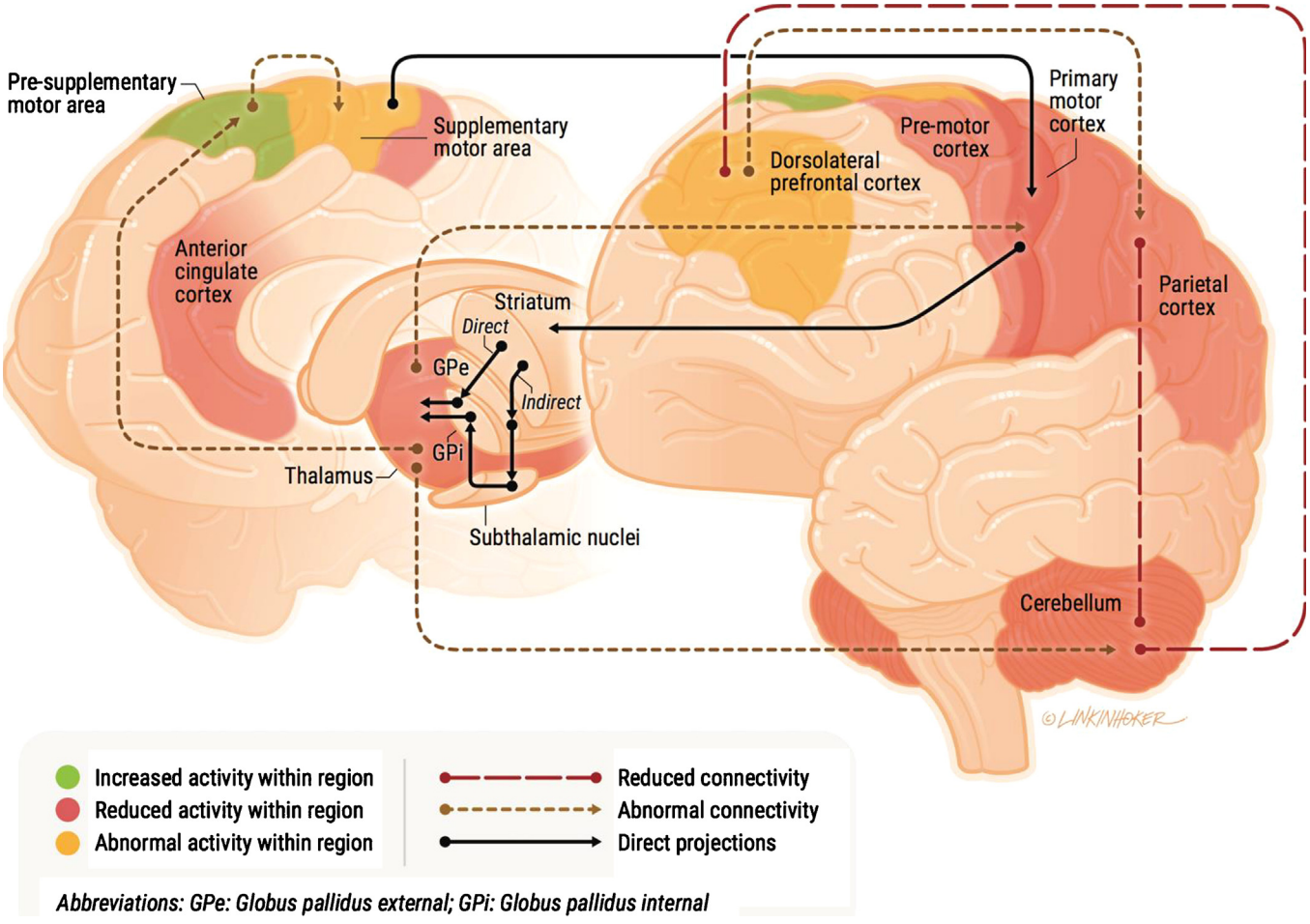

Fig. 1. A conceptual model of psychomotor slowing in psychosis.

2. Psychomotor slowing as an endophenotype and/or biomarker for psychosis

In the following sections, the current evidence for general psychomotor slowing (e.g., processing speed) in psychosis is reviewed before turning to research on the distinct cognitive and motor execution components contributing to slowing (see Table 1 for organizational terms). Within each section, findings that provide evidence for slowing being an endophenotype and/or biomarker for schizophrenia are reviewed. Consistent with a Research Domain Criteria approach (RDoC; [93]), we treat behavioral and biological findings of psychomotor slowing as "units of analysis" rather than independent constructs that are easily separable (see [94]). Thus, relevant behavioral and biological psychomotor findings are discussed together.

2.1. General psychomotor slowing in psychosis

For the purpose of this review, general psychomotor slowing will be defined as slowing on various measures of psychomotor slowing that do not differentiate amongst the various (i.e., cognitive) and motor processes that may be contributing to slowing when completing traditional assessments. It has been suggested that traditional measures of slowed processing speed in schizophrenia, such as the TMT- A and B and DSST, should primarily be considered as measures of higher-order cognitive processes (e.g., working memory, attention, visuospatial skills) rather than indices of psychomotor slowing because the execution of movement is not the principal task component [95]. However, given that slowing has been observed in both the cognitive and motor execution processes of these tasks in patients with psychosis [47,96], and they represent one of the most used neuropsychological assessments in the field, research examining processing speed abnormalities across the schizophrenia spectrum warrants discussion. Consistent with a staging model of schizophrenia, slowed processing speed is present in youth at clinical high-risk for the illness [25,97], and is well-evidenced in first-episode psychosis and patients with chronic schizophrenia [23,24,98]. Further, evidence from a wide array of robust research suggests that processing speed may be both an endophenotype and biomarker for schizophrenia.

2.1.1. General psychomotor slowing deficits as an endophenotype for psychosis

Evidence that psychomotor slowing is an endophenotype for psychosis would include findings demonstrating its association with the genetic liability for the illness. Candidate studies include research designs involving unaffected first-degree relative and twin populations, and findings in individuals with schizotypy or subclinical psychotic-like experiences in the general population. In a well-powered study of 147 patients with schizophrenia and 193 of their unaffected siblings, Egan et al. [99] found that healthy siblings of individuals with schizophrenia exhibited slower processing speed on the TMT-B than healthy controls which was associated with increased relative risk suggesting that slowed performance is familial and possibly heritable. This finding has been replicated in numerous studies using different psychomotor paradigms (e.g., TMT-A/B, Digit Symbol Coding Test [DST]) highlighting its robustness (see [100–102]). Further, similar results have been shown using extended pedigree research designs that do not select participants based on a single phenotype (i.e., schizophrenia) and instead randomly recruit large samples of both nuclear and extended families (e.g., first through fifth degree relatives) in order to examine genetic liability for psychosis [103,104]. Findings in monozygotic and dizygotic twins both concordant and discordant for schizophrenia have corroborated these family studies by showing that slowed processing speed is moderately genetically linked to schizophrenia [105].

Other evidence for psychomotor slowing as an endophenotype for schizophrenia comes from research on parkinsonian motor abnormalities (e.g., bradykinesia, slowed gait, akinesia) in unaffected first-degree relatives [106]. Kamis et al. [107] used transcranial ultrasound to examine the relationship between echogenicity of the basal ganglia and parkinsonian motor impairment in never-treated patients with schizophrenia and their unaffected first-degree relatives. Similar to findings in Parkinson's disease [108,109], both patients with schizophrenia and their relatives exhibited increased echogenicity of the substantia nigra compared to healthy controls and this hyperechogenicity was associated with more severe parkinsonian symptoms in both groups. Molina et al. [110] replicated this finding in a sample of neuroleptic-naïve schizophrenia patients and unaffected first-degree relatives, suggesting that parkinsonian motor deficits may be a key endophenotype for the illness that is associated with structural basal ganglia abnormalities. In another line of supporting evidence, slowed processing speed has been found in individuals in the general population with psychotic-like experiences (i.e., nonclinical psychotic symptoms such as fleeting hallucinations or mild social apathy) [111,112]. Critically, the severity of psychomotor slowing has been associated with the frequency and distress of both positive and negative psychotic-like experiences [111]. Taken together, although more direct research is required, the presence of psychomotor slowing in unaffected relatives and individuals with psychotic-like experiences in the general population suggests that slowing is not state dependent in psychosis.

2.1.2. General psychomotor slowing deficits as a biomarker for psychosis

Evidence that psychomotor slowing is a biomarker for psychosis would include findings demonstrating its association with the emergence, course (i.e., progression or remission), or severity of the illness. Candidate studies include research designs involving birth cohort studies, high-risk and first-episode populations with longitudinal follow-ups, and cross-sectional research examining associations with illness severity and pathophysiology. For instance, slowing in speed of processing at age 8 and declines in speed of processing from 8 to 11 were the strongest predictors of psychotic experiences at age 12 in a large birth cohort study in children [113]. Similarly, children that ultimately develop schizophrenia exhibit a slower rate of development in processing speed (as measured by the DST) compared to typically developing children [114], suggesting that deficits in psychomotor slowing may appear early developmentally and provide a useful marker for illness risk. Further, it has been shown that youth at clinical high-risk (CHR) for psychosis also have slowed processing speed that is at an intermediate level between controls and patients [25,100,115–117], and that this impairment predicts transition to psychosis [118–120]. Interestingly, CHR youth with slowing also exhibit resting state functional connectivity abnormalities that parallel those observed in schizophrenia (i.e., increased thalamocortical connectivity to M1) [121].

Consistent with findings in CHR youth, when comparing first-episode psychosis patients that performed within normal limits on a neuropsychological battery to first-episode patients with cognitive impairment, the cognitively normal subgroup performed similarly to controls in several cognitive domains but exhibited deterioration in processing speed (relative to premorbid levels) equivalent to the cognitively impaired subgroup [160]. This finding suggests that processing speed deterioration may be a core feature of the illness that is present in patients with and without general cognitive impairment. In addition, performance on speed of processing tasks with less reliance on externally guided action (e.g., TMT-A/B, etc.), such as verbal fluency (which requires internally guided action), has been shown to predict recovery and deterioration in first-episode patients [98,119]. After initial declines from the prodromal to first-episode stages of the illness, evidence suggests that slowed processing speed may remain relatively stable in chronic schizophrenia [122,123] but is still sensitive to deficits in social and role functioning over time [124].

Several other lines of converging evidence support the idea that psychomotor slowing is a putative biomarker for the illness. For example, actigraphy has been used to demonstrate that patients with schizophrenia

produce less volitional movement compared to healthy controls [81,125,126], which has been interpreted as reflecting overall motor slowing [127–129]. Further, less baseline volitional motor activity has been shown to predict the trajectory of negative symptoms at future psychotic episodes as well as deterioration across multiple episodes [126,130]. In fact, preliminary evidence suggests that across episodes, actigraphy patterns remain quite stable [130]. Using kinematic analysis of handwriting and structural MRI, it has been shown that CHR youth exhibit bradykinesia (i.e., slowed movement) when required to scale their velocity across shorter and longer targets distances, and that these deficits are associated with striatal volume and more severe positive and negative symptoms [131].

2.2. Distinct sub-processes contributing to psychomotor slowing in Schizophrenia

Taken together, there appears to be substantial evidence from a diverse array of methodologies and research designs to support the notion that general psychomotor slowing is not only a core feature of schizophrenia, but is also sensitive to disease processes, as well as the pathophysiology and genetic vulnerability for the disorder. However, the abovementioned findings are limited by their reliance on a single endpoint for quantifying psychomotor slowing (e.g., subjective ratings of motor behavior, time to finish a task) [132]. Specifically, the distinct cognitive and motor execution deficits contributing to psychomotor slowing are lost by collapsing across the various processes involved in action planning and motor execution, resulting in difficulty isolating the abnormal processes contributing to psychomotor slowing across the schizophrenia spectrum. Below, we review evidence for deficits in distinct areas of dysfunction in psychomotor slowing, as well as evidence that these deficits reflect endophenotypes or biomarkers for the illness.

Similar with past definitions [60], cognitive processes involved in comparing stimuli to previously learned stimulus-response mappings in working memory (i.e., response selection), decision making, inhibiting competing responses, volition, and motor planning and sequencing are referred to as the planning aspect of psychomotor slowing. In contrast, the processes implicated in the initiation, coordination, and execution of movements are interpreted as reflecting the motor execution sub-processes of psychomotor slowing. Here, evidence for distinct impairments across these processes are reviewed. One of the most common means for delineating the cognitive and motor processes of psychomotor slowing in schizophrenia has been the use of digitizing writing tablets to quantify the time required to complete different aspects of common neuropsychological measures of processing speed (e.g., TMT-A/B, DSST). A common application of this approach is to have participants complete the DSST on a writing tablet and measure the time it takes to match the digits to their corresponding symbols (i.e., planning) and the time spent writing the symbols (i.e., motor). In this and similar psychomotor tasks with writing tablets, impairments in planning have been found consistently, whereas results for motor execution time are more mixed [57,60,96]. Specifically, it is important to note that the motor execution deficits are not always present using similar methods [133], or across psychomotor tasks within studies [60,134].

Noticeable similarities emerge from event-related potential (ERP) studies of psychomotor slowing and research employing writing tablets. Using the lateralized readiness potential (LRP), a negative-going ERP observed over the motor cortex that indexes motor preparation when making left- versus right-hand motor responses, research has shown that schizophrenia patients exhibit deficits in both the cognitive and basic motor processes involved in simple and choice reaction time experiments [135–137]. Specifically, the LRP can be measured in two distinct ways that, when combined with an examination of LRP onset variability, provide unique information about the sub-processes contributing to psychomotor slowing (see [136]). For example, greater variability in the interval between the presentation of the stimulus and the onset of the LRP will result in reduced LRP amplitude that is the result of greater difficulty with selecting and planning a response. In contrast, greater variability in the interval between the onset of the LRP and the response will result in reduced LRP amplitude that is the result of greater difficulty executing a response. When comparing speeded to unspeeded responses, findings suggest that patients with schizophrenia were not able to modulate their speed across conditions and exhibited greater variability and reduced LRP in the interval between the stimulus and LRP onset, but not the interval between the LRP onset and response, suggesting that slowing is likely due to difficulties in response selection and planning rather than motor execution [136]. However, deficits in more basic motor execution processes have also been observed in patients with schizophrenia [135]. Thus, similar to the above-mentioned writing tablet studies, findings are inconsistent regarding whether the psychomotor slowing is primarily due to the cognitive or motor components of psychomotor processes. For example, Luck et al. [137] used the latency of the P300, an ERP index of the time required to perceive and categorize a stimulus, and the LRP to examine if psychomotor slowing on a simple reaction time task is largely due to deficits in stimulus categorization, response selection, or more basic motor processes. Findings generally indicated that patients with schizophrenia were equally as fast as controls when evaluating simple stimuli (i.e., no P3 latency group differences) and slowing was primarily the result of impairments in response selection rather than motor execution, as evidenced by longer latencies between stimulus onset and motor preparation rather than the interval between preparation and response. These findings are largely consistent with results from other studies using the LRP to examine psychomotor slowing in schizophrenia [136,138,139].

Taken together, impaired cognitive processes involved in response selection and motor preparation are consistently found in schizophrenia, whereas findings for motor execution are less consistent. Yet this interpretation is confounded due to the majority of the reviewed research using task paradigms that only require simplistic motor responses (e.g., button press, drawing lines or digits) rather than more taxing complex movements typical of everyday goal-directed behavior and fine motor control. Indeed, there is a large body of research suggesting that individuals across the schizophrenia spectrum exhibit slowing on a wide array of fine motor tasks including the grooved pegboard test [140,141], finger tapping [142–144], gait [145,146], and handwriting [147]. There are several possible reasons for mixed findings that are discussed in the following sections.

2.2.1. Deficits in distinct sub-processes of psychomotor slowing as endophenotypes for psychosis

Evidence that psychomotor slowing is an endophenotype for psychosis would include findings demonstrating its association with the genetic liability for the illness. Several studies have demonstrated that reaction times are prolonged in unaffected relatives of patients with schizophrenia [80,148,149], and there is some evidence to suggest that both the cognitive and motor components are implicated in this slowing. Regarding cognitive processes that may reflect a heritable vulnerability for the disorder, findings from functional MRI studies examining response selection in unaffected relatives suggests that abnormalities in neural regions associated with slowing in patients (See Fig. 1) show similar patterns in relatives [80,149,150].

Regarding specific evidence for slowing in motor execution as an endophenotype for psychosis, similar to research in schizophrenia, investigations using fine motor dexterity and motor speed (grooved pegboard, finger tapping) are the most common. For instance, differences have been found between controls and unaffected relatives on basic motor speed tasks (i.e., finger tapping) [151] and meta-analytic evidence suggests the overall effect size for finger tapping is small to moderate (d = .33) [152]. However, more work that examines complex motor execution is needed to better capture the extent that slowing of motor execution reflects the genetic liability for schizophrenia.

2.2.2. Deficits in distinct sub-processes of psychomotor slowing as biomarkers for psychosis

Evidence that psychomotor slowing is a biomarker for psychosis would include longitudinal and cross-sectional research designs demonstrating its association with the emergence, course (i.e., progression or remission), or severity of the illness. In a study by Grootens et al. [153], psychomotor slowing in recent-onset schizophrenia was examined using a writing tablet and the DSST along with a series of figure copying tasks that varied in complexity and found that patients with recent-onset schizophrenia were impaired in the planning phase of figure copying and that slowing increased with complexity. Notably, the observed slowing in planning processes in recent-onset schizophrenia were similar to that in chronic schizophrenia but less pronounced. Indeed, the slower planning on figure copying is associated with the severity of both positive [60], and particularly negative symptoms [60,96,154]. Further, several studies suggest that deficits across distinct sub-processes of psychomotor slowing may be limited to patients with pronounced negative symptoms [60,155], and may be sensitive to specific domains of negative symptoms such as apathy [96].

Regarding motor execution, evidence suggests increased movement slowing in chronic stages of schizophrenia and patients on neuroleptic medication. For example, patients with chronic schizophrenia performed significantly worse on measures of fine motor dexterity and motor speed compared to those with recent-onset psychosis [141], which is consistent with the finding that fine motor control deteriorates as the illness progresses [156,157]. Notably, there is also evidence that motor dexterity differentiates CHR youth that convert to formal psychosis from non-converters [158]. Lastly, meta-analytic findings suggest that both measures of processing speed (e.g., TMT-A/B, DSST) and motor dexterity (finger tapping, grooved pegboard) are sensitive to neuroleptic medication [159], suggesting that it may be possible that both the cognitive and motor components of psychomotor slowing can be used to monitor treatment effects. Taken together, characterizing the individual cognitive and motor contributions to slowing serves to inform the field's understanding of the specific deficits, and thus specific associations with the genetic vulnerability and pathophysiological mechanisms, underlying psychomotor slowing in schizophrenia. Further, sub-processes involved in planning responses seems to be particularly associated with negative symptoms in psychosis.

3. Conclusion

Evidence suggests that psychomotor slowing is present in unaffected first-degree relatives and twins, and is also associated with the frequency of psychotic-like experiences in the general population, indicating that psychomotor slowing may be a key endophenotype for schizophrenia. At the same time, general psychomotor slowing in psychosis also reflects a dose-dependent relationship across the different stages of the illness, with deficits becoming progressively worse from the prodromal stage to chronic schizophrenia. Furthermore, performance on various psychomotor tasks has been shown to predict recovery and deterioration in patients with schizophrenia, and was associated with both symptoms and relevant structural and functional abnormalities across the schizophrenia spectrum, indicating that psychomotor slowing may be a key biomarker for schizophrenia. Taken together, there appears to be substantial evidence from a diverse array of methodologies and research designs to support the notion that general psychomotor slowing is not only associated with the genetic vulnerability for the disorder, but is also a core feature of schizophrenia that is sensitive to disease processes and its pathophysiology.

Regarding distinct deficits across the "psychological" and motor components of psychomotor slowing, the reviewed evidence supports the conclusion that, although motor slowing is often observed, impairments in cognitive processes such as response selection and planning are the most consistent finding in the literature. This may be due to most research utilizing rather simple motor responses. Although the cognitive components of psychomotor slowing have received less attention in genetic vulnerability research in psychosis, similar findings regarding response selection and fine-motor dexterity have been demonstrated in unaffected relatives. Slowed planning was also demonstrated to be associated with both positive and negative symptoms. Further, performance on fine-motor dexterity tasks differentiated CHR youth that convert to psychosis from non-converters, is sensitive to antipsychotic medication, and is worse in chronic than recent onset schizophrenia. Taken together, there appears to be robust evidence that psychomotor slowing is both sensitive to the genetic vulnerability for schizophrenia (endophenotype) and disease processes (biomarker).

Future work on psychomotor slowing in schizophrenia should continue to disentangle the cognitive and motor components of slowing with a particular focus on using more complex motor movements. This will aid in determining the extent that the speed and fluency of a response contributes to slowing. Consistent with this goal, it will be critical for future research to focus on identifying the specific cognitive and motor processes that contribute to slowing. In regards to work on endophenotypes and biomarker research, more molecular genetic studies are needed to identify potential candidate genes associated with the various cognitive and motor processes contributing to psychomotor deficits. Similarly, neuroimaging studies optimized to differentiate the neural networks involved in distinct sub-processes of slowing and their association with the progression of the illness will help with biomarker development efforts. Together, this work would inform diathesis-stress models of psychosis and contribute to ongoing efforts to determine the etiology and development of schizophrenia.

Declaration of Competing Interest

None.

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