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P300 in Schizophrenia: Then and Now

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In 1965, Sutton and colleagues described the P300 component of the EEG-based evoked potential that was affected by stimulus uncertainty; that is, a larger P300 amplitude was associated with a failure to accurately predict the sensory modality of the next event (Sutton et al., 1965). Until that time, evoked potentials were primarily used to assess the integrity of sensory pathways. However, the P300 component, a positive-going wave that reaches its peak amplitude at approximately 300ms, was shown to reflect a cognitive process and could be elicited even when a stimulus was omitted in a sequence of repeated stimulus presentations. Evoked potentials then acquired a new name: event-related potentials (ERPs). Critically, P300 was recognized to be an electrophysiological brain measure that could be applied within cognitive psychology, providing a promising opportunity to study a disease with cognitive manifestations, like schizophrenia.

A few years later, Roth and Cannon were the first to report that P300 amplitude was reduced in people with schizophrenia relative to healthy individuals (Roth & Cannon, 1972). Around that same time, the Sutton lab reported a similar finding (Levit et al., 1973). These studies initiated a 50-year run of studies of P300 in schizophrenia, first with the hope of providing an objective diagnostic test, and later, with the goal elucidating pathophysiological processes operating over the illness course of schizophrenia as well as prior to illness onset in youth at clinical high risk for psychosis.

In this article, we begin by providing a basic introduction to the P300 component of the ERP followed by a brief review of what is known about P300 in schizophrenia after over 50 years of research. We then focus on more recent efforts to expand our knowledge of P300 beyond its sensitivity to schizophrenia itself to its

potential role as a biomarker of clinical or genetic vulnerability for psychosis. We also describe efforts to better understand P300 within the context of the significant clinical heterogeneity among individuals with schizophrenia. Finally, we describe a few recent avenues of research that extend beyond measuring the traditional P300 ERP component in people with schizophrenia that may further help elucidate specific cognitive mechanisms that are disrupted. We close by discussing several promising areas for future research on P300 and schizophrenia.

A BRIEF OVERVIEW OF P300

Early studies of P300 largely focused on determining how ERP signatures varied according to stimulus features (Sutton et al., 1965; Sutton et al., 1967) and ultimately revealed the critical role of stimulus probability and task relevance in the generation of P300. These studies laid the foundation for the development of the "oddball" paradigm (Donchin, 1981; Duncan-Johnson & Donchin, 1977; Pritchard, 1981), which has been the most common approach to measuring P300. In the oddball paradigm, P300 is elicited by behaviorally relevant or salient infrequent stimuli that are presented within a stream of frequent "standard" stimuli. While the cognitive significance of P300 continues to be debated, prevailing views consider it to reflect attentional resource allocation (Polich, 1989b), phasic attentional shifting (Knight, 1991), the updating of stimulus context in working memory (Donchin & Coles, 1988), or stimulus salience (Sutton et al., 1967). The latency of P300 is thought to reflect processing speed or stimulus classification efficiency (Duncan-Johnson & Donchin, 1977; Kutas et al., 1977) independent of motor preparation or behavioral response time (Duncan-Johnson, 1981; McCarthy & Donchin, 1981).

In 1975, Squires and colleagues described two distinct subcomponents of the P300 elicited during the oddball paradigm that differ in their psychological antecedents, scalp topography, and latency (Squires et al., 1975). The P3b is elicited when the infrequent stimulus is a target that requires a voluntary response, such as a button press or the maintenance of a mental running count of targets presented, thus relying on a “top-down” shift of attention or an updating of memory. The P3b is maximal at midline parietal electrodes, peaks about 300-350ms following simple target stimulus onset (Polich, 1990; Squires et al., 1975), and is commonly referred to as the “target P3b.” P3a, on the other hand, is elicited by infrequent novel or otherwise salient non-target distractor stimuli that require no response, and reflects involuntary, phasic “bottom-up” attention necessary for rapid detection, evaluation, and adaptation to unexpected and potentially important changes in the environment (Daffner et al., 2000). P3a, often called the “novelty P3” when elicited by novel stimuli, occurs approximately 50ms earlier than P3b and is maximal over frontocentral electrodes. Regarding their neural sources, lesion and depth electrode studies have linked P3a to prefrontal cortical generators as well as the anterior cingulate cortex, while P3b has generally been localized to temporal-parietal regions (Halgren et al., 1998; Knight et al., 1989; Soltani & Knight, 2000; Wronka et al., 2012). Since the identification of these subcomponents, studies of P300 have primarily implemented two-stimulus oddball paradigms, in which infrequent target *or* non-target novel/distractor stimuli are interspersed among standard stimuli, but some have also implemented three-stimulus oddball paradigms that include *both* infrequent target and non-target novel stimuli during which participants are instructed to respond to the targets and ignore the novel stimuli.

THE ‘BROKEN P300’ IN SCHIZOPHRENIA

The five decades of P300 studies in patient samples, with most implementing a variant of the oddball paradigm, have confirmed P300 amplitude reductions and latency delays in schizophrenia (see meta-analyses by Bramon et al., 2004; Jeon & Polich, 2003). To this day, P300 amplitude reduction continues to be considered one of the most replicable biological reflections of schizophrenia.

The majority of studies to date have demonstrated that auditory P300 is more likely to be reduced than visual P300 in schizophrenia (Jeon & Polich, 2003). However, P300 elicited by visual stimuli has also been shown to be reduced (Brecher et al., 1987; Hamilton, Woods, et al., 2019; Lee et al., 2010; Mathalon et al., 2010; Oribe et al., 2015; Strandburg et al., 1994; van der Stelt et al., 2004; but see Mathalon, Ford, & Pfefferbaum, 2000; Shelley et al., 1996). In direct comparisons, auditory P300 amplitude tends to show a larger reduction than visual P300 in schizophrenia (Egan et al., 1994; Mathalon, Ford, & Pfefferbaum, 2000; Pfefferbaum et al., 1989; but see Hamilton, Woods, et al., 2019), consistent with greater abnormalities attending to auditory relative to visual information. While most of these prior studies have focused on target P3b amplitude in schizophrenia, studies of P3a have also shown amplitude reductions in response to infrequent novel or salient stimuli in both auditory (Ford et al., 1999; Hamilton, Woods, et al., 2019; Mathalon, Ford, & Pfefferbaum, 2000; Perlman et al., 2015a) and visual (Bestelmeyer et al., 2009; Hamilton, Woods, et al., 2019) modalities.

Given the consistency with which findings of P300 amplitude reduction in schizophrenia have been reported, it has generally been thought to reflect a stable

trait marker of the illness, a conclusion also supported by findings of trait-like stability of P300 deficits in longitudinal studies (Blackwood et al., 1987; Mathalon, Ford, Rosenbloom, et al., 2000; Turetsky et al., 2000). However, P300 also shows some amplitude changes in association with fluctuations in clinical state/symptom severity over the illness course of schizophrenia (Ford et al., 1999; Mathalon, Ford, & Pfefferbaum, 2000). Indeed, in a study of both state and trait effects, P3a and P3b both tracked clinical state over time independent of medication status (Mathalon, Ford, & Pfefferbaum, 2000). Moreover, P3a and P3b remained reduced in patients whose symptoms had improved (Mathalon, Ford, & Pfefferbaum, 2000). In addition, P300 amplitude reduction and latency prolongation have been observed to worsen with longer duration of illness (Mathalon, Ford, Rosenbloom, et al., 2000; O'Donnell et al., 1995), consistent with progressive pathophysiological processes operating over the course of schizophrenia. These findings underscore the fact that some aspects of the variance of P300 in schizophrenia are attributable to trait-like deficits, some to the clinical state at the time of recording, and some to the stage of the illness. These properties are not mutually exclusive.

What affects P300 in people with schizophrenia?

Stimulus/task variables? Despite a large body of research in healthy participants (e.g., Polich, 1987, 1989a; Polich, 1990; Squires et al., 1976), relatively few studies have systematically evaluated whether specific task parameters or other stimulus-related variables affect P300 in people with schizophrenia. Several studies have shown lower target stimulus probability (Duncan-Johnson et al., 1984; Duncan et al., 1987; Ford, 1999) and shorter interstimulus intervals (Gonsalvez et al., 1995; Jeon & Polich, 2003; Mathalon & Ford, 2002; Roth et al., 1991) result in greater differences in P3b amplitudes and latencies between schizophrenia and

healthy participants. Moreover, shorter tone durations during auditory oddball paradigms have been associated with larger differences between schizophrenia and healthy participant groups (see Jeon & Polich, 2003). With regards to P3a, people with schizophrenia show amplitude reductions in response to infrequently presented distractor stimuli that are non-novel, such as tones and noise bursts (e.g., Hermens et al., 2010; Jahshan, Cadenhead, et al., 2012; Jahshan, Wynn, et al., 2012; Kaur et al., 2011; Mathalon, Ford, & Pfefferbaum, 2000; Rissling et al., 2012) as well as perceptually novel distractor sounds, such as a dog barking or a car horn honking (e.g., Hamilton et al., 2018; Hamilton, Woods, et al., 2019) within an oddball sequence.

Effort and attention? Early evidence suggested that P300 remains reduced in people with schizophrenia even when the oddball paradigm is presented passively with no task demands (Pfefferbaum et al., 1989). This was followed by several studies showing that P3a amplitudes, in particular, remain reduced during passive auditory oddball paradigms during which attention is directed elsewhere entirely (Hermens et al., 2010; Jahshan, Cadenhead, et al., 2012; Jahshan, Wynn, et al., 2012; Kaur et al., 2011; Rissling et al., 2012). However, some have suggested that P300 amplitudes may be somewhat augmented by increased effort or motivation (Brecher & Begleiter, 1983; Fukuda et al., 1997; but see Salisbury et al., 1994). Although participants with schizophrenia do not sustain attention as consistently as healthy individuals, when participants are attending to the stimuli, P300 amplitude remains reduced (Ford, White, Lim, et al., 1994). Nonetheless, enhancements in attention by incidental emotional stimuli have been shown to improve visual P300 amplitudes in schizophrenia (Horan et al., 2012), suggesting that many stimulus

characteristics can modulate P300 amplitude in schizophrenia similarly to their effects in healthy individuals.

Antipsychotic medications? Generally, antipsychotic medications appear to have relatively little influence on P300. A meta-analysis of studies through 2003 found that effect sizes of the P300 deficit in schizophrenia did not differ between studies of medicated versus studies of unmedicated people (Ford, White, Csernansky, et al., 1994; Jeon & Polich, 2003). Moreover, a comparison of high medication dose, low medication dose, and no medication groups resulted in no group differences in P300 (Jeon & Polich, 2003). Although some individual studies have suggested that antipsychotic medications may increase P3b amplitude (Asato et al., 1996; Coburn et al., 1998), the deficits are not eliminated by the medication (Mathalon, Ford, & Pfefferbaum, 2000) and worsen after antipsychotic medications are withdrawn (Faux et al., 1993).

EFFORTS TO MOVE P300 RESEARCH BEYOND THE TRADITIONAL DSM 'SCHIZOPHRENIA' DIAGNOSIS

Broadening the search.

In recent decades, efforts have been made to determine whether P300 may be a useful measure of vulnerability for developing schizophrenia; that is, whether it may indicate the likelihood of developing psychosis or reflect a genetic vulnerability for the illness.

P300 in individuals at clinical high risk for psychosis

With the development and validation of clinical criteria to prospectively identify young people at clinical high risk for psychosis (CHR-P), several studies

have sought to determine whether P300 abnormalities predate and predict psychosis onset in order to (1) improve clinical outcome prediction among CHR-P individuals, and (2) help clarify mechanisms associated with the pathogenesis of schizophrenia. Studies of CHR-P individuals, who experience attenuated, or less often, very brief, symptoms of psychosis or have genetic risk for psychosis accompanied by a recent decline in psychosocial functioning, have demonstrated reduced P3b amplitudes to auditory (Bramon et al., 2008; del Re et al., 2015; Frommann et al., 2008; Fusar-Poli et al., 2011a, 2011b; Hamilton, Roach, et al., 2019; Hamilton, Woods, et al., 2019; Ozgurdal et al., 2008; van der Stelt et al., 2005; van Tricht et al., 2010) and to a lesser extent, visual (Hamilton, Woods, et al., 2019; Oribe et al., 2013), target stimuli during the oddball paradigm. Indeed, a few studies that included a schizophrenia comparison group suggest that the magnitude of P300 deficits in CHR-P individuals and schizophrenia patients are similar (del Re et al., 2015; Hamilton, Woods, et al., 2019; Oribe et al., 2013). Of the fewer studies that have examined P3a, CHR-P individuals have also shown reduced auditory (Atkinson et al., 2012; del Re et al., 2015; Hamilton, Roach, et al., 2019; Hamilton, Woods, et al., 2019; Jahshan, Cadenhead, et al., 2012; Lepock et al., 2019; Mondragon-Maya et al., 2013; but see Atkinson et al., 2017) and visual (Hamilton, Woods, et al., 2019; Lee et al., 2010; Oribe et al., 2020) P3a amplitudes in response to novel or unattended distractor stimuli.

P300 also appears to be associated with future clinical outcomes in CHR-P individuals followed longitudinally. In particular, P3b amplitudes may predict future psychosis onset, with future CHR-P converters exhibiting amplitude deficits relative to CHR-P nonconverters to target tones (Hamilton, Roach, et al., 2019; Hamilton, Woods, et al., 2019; van Tricht et al., 2011; van Tricht et al., 2010) or target visual

stimuli (Hamilton, Woods, et al., 2019). Furthermore, more deficient P3b amplitude predicts a shorter time to psychosis onset when elicited by both auditory (Hamilton, Roach, et al., 2019; Hamilton, Woods, et al., 2019; van Tricht et al., 2010) and visual (Hamilton, Woods, et al., 2019) stimuli. Importantly, analysis of data collected as part of the largest consortium of CHR-P individuals to date showed that larger auditory P3b amplitudes were associated with future *remission* from the CHR-P syndrome; indeed, CHR-P individuals who had remitted by the two-year follow up assessment had baseline P3b amplitudes that were indistinguishable from those of healthy controls. Although another study did not observe a similar remission effect among CHR-P individuals, they did document an association between greater baseline P3b amplitudes and improvement in negative and general psychopathology symptoms (Kim et al., 2015).

Regarding P3a amplitudes and future clinical outcomes in CHR-P individuals, the relatively few existing studies have yielded mixed results. Although one study has reported that smaller P3a amplitudes predict conversion to psychosis and larger amplitudes predict remission from the psychosis risk state (Tang et al., 2019), others have failed to show P3a amplitudes to differentiate future converters from nonconverters (Atkinson et al., 2017; Hamilton, Roach, et al., 2019; Hamilton, Woods, et al., 2019) or predict the time to psychosis onset when elicited by auditory (Hamilton, Roach, et al., 2019; Hamilton, Woods, et al., 2019) or visual (Hamilton, Woods, et al., 2019) stimuli, instead being reduced in CHR-P individuals irrespective of their clinical outcomes (Hamilton, Roach, et al., 2019).

Family studies of P300

P300 has also been proposed as an endophenotypic marker that could provide a neurophysiological bridge between genetic risk and phenotypic expression of schizophrenia (Bramon et al., 2005; Turetsky et al., 2007; Turetsky et al., 2015). Several twin studies have demonstrated the heritability of P300 abnormalities (Bestelmeyer et al., 2009; Hall et al., 2009; O'Connor et al., 1994), and heritability has been estimated at 68–80% for P300 amplitude and 21–56% for P300 latency (Hall et al., 2009; Hall et al., 2006). Other family studies have demonstrated P300 amplitude reductions among unaffected relatives of people with schizophrenia (see Bramon et al., 2005; Earls et al., 2016), including reductions in both P3b (Bestelmeyer et al., 2009; Groom et al., 2008) and P3a (Turetsky et al., 2009; Turetsky et al., 2000). Indeed, the most recent meta-analysis of 20 family studies indicated reliable deficits in P300 amplitude and latency in unaffected relatives relative to healthy controls, although to a lesser extent than in people with schizophrenia (Earls et al., 2016).

Although results from family studies are consistent with abnormal P300 reflecting genetic risk for psychosis and its potential role as a genetic endophenotype (Turetsky et al., 2007; Turetsky et al., 2015), less is known regarding the actual genetic basis of P300 amplitude reductions in schizophrenia. Studies of specific candidate genes (e.g., DISC1, COMT) have suggested associations with reduced P300 amplitudes in schizophrenia (Blackwood et al., 2001; Gallinat et al., 2003; Shaikh et al., 2013; Wang et al., 2009), and several more genome-wide association studies have also linked P300 abnormalities to disrupted genetic markers that have been implicated in the pathogenesis of schizophrenia or its symptoms (Decoster et al., 2012; del Re et al., 2014; Hall et al., 2014). However, other large sample studies have failed to find such genetic links (Bramon et al.,

2006; Liu et al., 2017). Despite considerable evidence supporting the heritability of P300 deficits and initial studies demonstrating genetic links to P300 abnormalities in schizophrenia, replication remains an issue for identifying specific genetic contributions to disrupted P300 in schizophrenia (see Owens et al., 2016). Very large samples may ultimately be needed to reveal any subtle associations between schizophrenia risk genes and P300 (Bramon et al., 2006; Liu et al., 2017).

Of note, a few studies in the general population have also reported an association between reduced P300 amplitudes and schizotypal features (Davidson et al., 2018; Deng et al., 2023; Klein et al., 1999), which may reflect a genetic vulnerability for psychosis (e.g., Lenzenweger, 2018).

Narrowing the search

Although the use of DSM-defined categorical psychiatric disorders can facilitate patient care and research into phenomenologically defined discrete clinical disorders, there is considerable heterogeneity among individual clinical presentations and illness courses. This seems to be especially true of schizophrenia, and it may hinder efforts to better understand the mechanisms underlying its development and course. Rather than a diagnosis-oriented approach, a symptom-oriented one enables investigations of specific mechanisms that may underlie specific symptoms and lead to more targeted treatment strategies.

Unfortunately, investigations into the relationships between specific schizophrenia symptom domains and P300 have been largely inconsistent. Some studies have shown P3b amplitudes to be associated with more severe psychosis symptoms (e.g., del Re et al., 2015; Egan et al., 1994; Jeon & Polich, 2003; Mathalon, Ford, & Pfefferbaum, 2000). Others, however, have also shown

associations with disorganization (e.g., Havermans et al., 1999; Higashima et al., 1998; Perlman et al., 2015a), negative symptoms (e.g., Andersen et al., 2016; Bruder et al., 2001; Kim et al., 2014; Mathalon, Ford, & Pfefferbaum, 2000; Perlman et al., 2015a; Pfefferbaum et al., 1989; Strik et al., 1993), and social and occupational functioning (Hermens et al., 2010; Perlman et al., 2015a). Others still have failed to demonstrate associations with symptoms (e.g., Ford, 1999; Frodl-Bauch et al., 1999) and functioning (Hamilton et al., 2018). Similarly, specific studies of P3a have suggested that reduced amplitude has been associated with the presence of auditory hallucinations (Antonova et al., 2021; Fisher et al., 2010; Fisher et al., 2014), more severe negative symptoms in patients (Merrin & Floyd, 1994), and psychosocial function status (Light et al., 2015), but results have also been mixed (Giordano et al., 2021; Hamilton et al., 2018; Perlman et al., 2015a). Such inconsistencies may be accounted for, in part, by restricted ranges of symptoms evident in particular patient groups (Mathalon & Ford, 2012) and task parameters; for example, it appears that reduced P3a amplitude elicited during a passive auditory oddball task during which attention is directed elsewhere may be associated with poorer functioning (Hermens et al., 2010; Light et al., 2015), but it may not be when P3a is elicited during active attention-mediated target detection tasks (Hamilton et al., 2018; Perlman et al., 2015b; but see Giordano et al., 2021). However, associations between P300 and clinical variables have differed even among studies using identical tasks and stimulus parameters, suggesting that other factors such as illness acuity (Eikmeier et al., 1992) and a broad range of symptom measurement challenges and confounding clinical variables (Mathalon & Ford, 2012) may also contribute to inconsistent results. It is noteworthy that many studies

do not report any findings at all, possibly because the results were null or the tests were not done.

In addition to clinical symptoms, significant cognitive impairment is highly prevalent among people with schizophrenia (Bora et al., 2010; Gold & Harvey, 1993; Heinrichs & Zakzanis, 1998). However, similar to symptom correlations, P300 and cognitive function among people with schizophrenia have been inconsistently correlated, with variable correlations reported across a broad range of cognitive domains. Some have observed poorer learning and memory performance, particularly verbal memory performance, to be associated with greater P3b amplitude reduction (Kim et al., 2003; Nieman et al., 2002; Shajahan et al., 1997) and latency delay (Souza et al., 1995). Others have reported P3b associations with attention (Kruiper et al., 2019; Morales-Munoz et al., 2017), executive function (Dichter et al., 2006), working memory (Kruiper et al., 2019), speed of processing (Dichter et al., 2006), and social cognitive functions (Jahshan et al., 2013). Similarly, P3a amplitude reductions have been associated with poorer performance on tests of attention (Hermens et al., 2010; Rissling et al., 2013), verbal learning (Hermens et al., 2010), and even social cognition (Jahshan et al., 2013), while others have failed to find direct relationships with a range of cognitive functions (Koshiyama et al., 2021; Kruiper et al., 2019).

EFFORTS TO MOVE BEYOND P300 IN SCHIZOPHRENIA: TOWARD A MORE NUANCED VIEW

Efforts to extend beyond the traditional approach to studying P300 in schizophrenia may yield additional mechanistic insights. We describe three such efforts below.

Single trial and time-frequency analysis of P300

In 1994, we asked if reductions in P300 were due to (1) small P300s on some trials but normal P300s on others, perhaps reflecting the waxing and waning of attention within a testing session, or (2) small P300s on all trials, perhaps reflecting limitations of available resources, or (3) individual P300s occurring at variable latencies, perhaps reflecting variable strategies of speed and accuracy. In a single trial analysis of the P300, we used a delta-band half-sine wave as a "P300 template" and fitted it to the EEG following a target tone. We determined whether there was a P300 in the single trial, and if so, we estimated its latency and amplitude. In so doing, we were able to determine that all three were true; people with schizophrenia had fewer, smaller, and more variable latency P300s (Ford, White, Lim, et al., 1994).

This could be viewed as an initial time-frequency analysis of power and intertrial synchrony of data in the delta band. With the advent of sophisticated EEG time-frequency analysis algorithms in 2007, we asked whether these reductions could be accounted for by deficits in power or synchrony at a range of specific frequencies. We reported that P300 amplitude and both delta and theta power and synchrony were reduced in people with schizophrenia relative to healthy individuals; furthermore, delta power and synchrony better distinguished between groups than P300 amplitude (Ford et al., 2008). Other studies have similarly reported dependence of P300 on delta and theta activity in studies of people with schizophrenia (e.g., Almeida et al., 2011; Doege et al., 2009; Ergen et al., 2008;

Shin et al., 2010). Extending these findings, Wu and colleagues recently found reductions in delta band power and synchrony in CHR-P youth (Wu et al., 2022).

P300 to standard stimuli

As noted above, an important factor in P300 generation is stimulus probability, with P300 reflecting “surprise” induced by a violation of expectancy (Donchin, 1981; Duncan-Johnson & Donchin, 1977). To the extent that a participant is aware of the context set up by local probabilities, an expectation may be established for one event or another. A violation of this expectancy will elicit a P300 (Duncan-Johnson & Donchin, 1977; Squires et al., 1976). Accordingly, while P300 has typically been elicited by infrequent target or novel distractor stimuli, standard stimuli can actually elicit a P300 if they are relatively unlikely to occur within local sequences of standards (Gilmore et al., 2005; Stadler et al., 2006). That is, the implicit context created by local stimulus probabilities can render standard stimuli improbable, and therefore, deviant. In our auditory oddball paradigm, although the global probability of a standard tone was p=.70, the sequential probability of a standard varied from p=1.0 to .16 (Ford et al., 2010). We showed that standards appearing later in local sequences of repeating standards during an auditory oddball task actually elicited a P3a, suggesting that healthy individuals implicitly process local sequential probabilities of oddball task stimuli. In other words, healthy individuals developed the expectation that it was “time for a change” (i.e., that it was time for a target or novel stimulus to occur) and when the change did not occur, their expectations were violated. Interestingly, no such P3a was evident in schizophrenia patients (Ford et al., 2010). This failure to implicitly process local sequential probabilities suggests that people with schizophrenia are deficient in

using the implicit context established by what is recent in stimulus history to anticipate that an otherwise standard stimulus was unlikely and its occurrence unexpected.

Modeling schizophrenia effects on P300 via pharmacological challenge

N-methyl-D-aspartate receptor (NMDAR) hypofunction has been implicated in the pathophysiology of schizophrenia in large part due to pharmacological challenge studies in healthy individuals showing that administration of NMDAR antagonist drugs, such as ketamine, induce symptoms, cognitive deficits, and neurophysiological changes similar to those observed in schizophrenia (e.g., Krystal et al., 2002; Moghaddam & Javitt, 2012; Moghaddam & Krystal, 2012). Several studies have now indicated that ketamine administration to healthy individuals results in both P3b and P3a amplitude reductions (Gunduz-Bruce et al., 2012; Mathalon et al., 2014; Oranje et al., 2009; Oranje et al., 2000; see Schwertner et al., 2018) that are similar to the deficits observed in schizophrenia (Hamilton, Ford, et al., 2019). These findings suggest that glutamatergic neurotransmission at NMDARs may contribute to P300 generation and are consistent with involvement of NMDAR hypofunction in schizophrenia in mediating P300 abnormalities. Of note, however, challenge studies in healthy individuals have also linked P300 to noradrenergic (Nieuwenhuis et al., 2005), dopaminergic (Polich, 2007), catecholaminergic (Polich & Criado, 2006), and GABAergic (Watson et al., 2009) systems, as well as serotonin 5-HT2A (Umbricht et al., 2003), cholinergic muscarinic (Brown et al., 2015) and cannabinoid receptor functions (D'Souza et al., 2012; Roser et al., 2008). Indeed, early studies suggested that the P3a is modulated by dopaminergic/frontal function, whereas P3b is affected by norepinephrine/parietal processes (Polich, 2007; Polich &

Criado, 2006). Therefore, several interacting neurotransmitter systems, including the NMDAR/glutamate system, are likely to contribute to P300 modulation in schizophrenia (Frodl-Bauch et al., 1999; Warren et al., 2023).

CONCLUSIONS: What we now know and future directions

In 50 years of P300 research in schizophrenia, the findings reported by Roth and Cannon (Roth & Cannon, 1972) have been replicated and expanded. For example, we now know much more about the experimental variables that affect P300 reduction in schizophrenia. To the extent that P300 reflects the ongoing updating of context, regardless of whether explicit attention is paid, its reduction in schizophrenia can now be understood to reflect deficits in context updating, such that people with schizophrenia may fail to use the implicit context established by recent history to anticipate future events. Given some identified associations between P300 and performance on cognitive tests, these deficits may be associated with cognitive functions such as attention and memory, although further research is needed to clarify the mechanisms of any downstream effects on specific domains of cognition. Indeed, efforts to identify correlations with specific cognitive functions that are the targets of current treatment development efforts may prove more useful than associations with gross measures of clinical symptoms (Luck et al., 2011).

Predicting outcomes in the CHR-P population with P300 amplitude is also a major advance in the field and may indicate that the psychological and biological mechanisms underlying abnormal P300 contribute to the clinical course of psychosis among at-risk young people. Further, the intact ability to effectively

recruit attentional resources may even afford some protection against the progression of psychosis. Importantly, these findings also suggest that P300 may be used as a biomarker that can augment clinical information for individualized risk prediction and may support future efforts to develop clinical staging algorithms that match aggressiveness of CHR-P treatment with prognostic indicators, ultimately helping to optimize individualized care (Mathalon, 2011; McGorry et al., 2007; Wood et al., 2011). More large scale studies that replicate these findings are needed to more definitively establish the predictive utility of P300; the potential for P300 to contribute to predictive algorithms combining other biological and clinical measures remain unexplored and warrant future study as well. Moreover, although we know P300 reduction in schizophrenia runs in families, larger genetic association studies are needed to clarify whether deficient P300 and its associated mechanisms are linked to specific risk loci for schizophrenia.

We also now know that glutamate transmission at NMDARs contribute to P300, and modeling hypothesized NMDA receptor hypofunction in schizophrenia using NMDAR antagonist drugs pharmacological challenge studies with healthy volunteers reproduce the P300 deficits seen in schizophrenia, consistent with the NMDAR hypofunction model. These findings need to be explored in more depth with pharmacologic challenges targeting other neurotransmitter systems, both in humans and in animal models of schizophrenia, to broaden our search for treatment targets.

Recent studies also suggest that time-frequency analyses of P300 may increase its sensitivity to schizophrenia, which will also likely be useful in future rodent studies of P300 (Richard et al., 2017) geared toward treatment development. We encourage neurophysiologists working with rodents to use P300 to bridge the

445 species gap so that it can be used for treatment development and even as a marker
446 of illness course and symptom improvement in rodent models of schizophrenia. A
447 key first step is to explore the parameters that we have laid out here that control
448 P300 until a rodent paradigm is available that elicits a P300 that obeys the rules
449 established in human studies.
450 Taken together, the large body of research to date continues to support P300
451 as a key bridge between biology and psychology in schizophrenia (Ford, 1999) and
452 highlights the potential role of P300 as a prognostic biomarker of psychosis and as a
453 target that could be used to accelerate treatment development efforts in future
454 translational studies.

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