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Neurodevelopmental vulnerability to psychosis: Developmentally-based methods enable detection of early life inhibitory control deficits that predict psychotic-like experiences at the transition to adolescence

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Abstract

Background—Inhibitory control develops in early childhood, and atypical development may be a measurable marker of risk for the later development of psychosis. Additionally, inhibitory control may be a target for intervention.

Methods—Behavioral performance on a developmentally appropriate Go/No-Go task including a frustration manipulation completed by children ages 3–5 years (early childhood; n=107) was examined in relation to psychotic-like experiences (PLEs; “tween”; ages 9–12), internalizing symptoms, and externalizing symptoms self-reported at long-term follow-up (pre-adolescence; ages 8–11). ERP N200 amplitude for a subset of these children (n=34) with electrophysiological data during the task was examined as an index of inhibitory control.

Results—Children with lower accuracy on No-Go trials compared to Go trials in early childhood ($F(1,101)=3.976$, $p=.049$), evidenced higher PLEs at the transition to adolescence 4–9 years later,

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Ethical Considerations

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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reflecting a specific deficit in inhibitory control. No association was observed with internalizing or externalizing symptoms. Decreased accuracy during the frustration manipulation predicted higher internalizing, $F(2,202)=5.618$, $p=.004$, and externalizing symptoms, $F(2,202)=4.663$, $p=.010$. Smaller N200 amplitudes were observed on No-Go trials for those with higher PLEs, $F(1,101)=6.075$, $p=.020$; no relationship was observed for internalizing or externalizing symptoms.

Conclusions—Long-term follow-up demonstrates for the first time a specific deficit in inhibitory control behaviorally and electrophysiology, for individuals who later report more PLEs. Decreases in task performance under frustration induction indicated risk for internalizing and externalizing symptoms. These findings suggest that pathophysiological mechanisms for psychosis are relevant and discriminable in early childhood, and further, suggest an identifiable and potentially modifiable target for early intervention.

Keywords

Inhibitory control; psychopathology; psychosis; early childhood; adolescence; ERP

Emerging psychopathology in early adolescence is prevalent, with psychiatric disorders affecting approximately one in five adolescents (Costello, Copeland, & Angold, 2011). During the early stages of psychopathology, pluripotent signs of risk are often characterized by general psychopathology and distress, rather than domain-specific symptoms (McGorry, Hartmann, Spooner, & Nelson, 2018). These indicators of risk are influenced by the development of inhibitory control and environmental expectations in early childhood, manifest in behavior, and could be measurable (Bowie, 2010). Inhibitory control deficits have been strongly linked to impairing and treatment-resistant negative symptoms in schizophrenia-spectrum disorders (Doege et al., 2010; Mittal et al., 2016). Identifying the neurodevelopmental precursors of these deficits would provide the opportunity to focus intervention efforts on prevention of the developmental cascade leading to later psychopathology instead of rehabilitation. However, little is known about the predictive power of inhibitory control as related to risk for schizophrenia-spectrum disorders and whether risk can be identified through inhibitory control dysfunction in early childhood.

Inhibitory control is an ideal candidate for identifying risk for psychopathology broadly and for identifying discrete profiles of risk because it is implicated in schizophrenia and common internalizing and externalizing syndromes [e.g., anxiety and oppositional disorders, among others (McTeague, Goodkind, & Etkin, 2016; Shanmugan et al., 2016)]. However, the type of disruption varies by diagnosis type (Goschke, 2014; Nelson, Strickland, Krueger, Arbisi, & Patrick, 2016) and may be a key mechanism differentiating among risk for different symptom domains (Shanmugan et al., 2016). As previously mentioned, inhibitory control deficits are frequently present in schizophrenia-spectrum disorders(Doege et al., 2010; Mittal et al., 2016). In contrast to psychosis, internalizing disorders are linked with high levels of inhibitory control (Goschke, 2014; Kooijmans, Scheres, & Oosterlaan, 2000; White, McDermott, Degnan, Henderson, & Fox, 2011). Conversely, externalizing disorders are characterized by reduced inhibitory control (Kooijmans et al., 2000; Schachar & Logan, 1990; Utendale & Hastings, 2011).

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In addition to the conceptual importance, inhibitory control can easily be measured behaviorally and is indexed by the event-related potential (ERP) N200 component (Chikara, Komarov, & Ko, 2018; Rueda-Delgado et al., 2021). Electroencephalography (EEG) data used to generate ERPs can be collected with both adults and children, provided developmentally appropriate adjustments are made (Brooker et al., 2020). In addition to the robust links between inhibitory control and schizophrenia-spectrum disorders behaviorally, (Gotra et al., 2020; Mittal et al., 2016) there is also a relationship with reduced N200 amplitudes to no-go trials (Doege et al., 2010; Groom et al., 2008). Internalizing problems have been linked with a lack of difference in N200 amplitudes across go and no-go trials (Hum, Manassis, & Lewis, 2013) or increased N200 amplitudes (Moadab, Gilbert, Dishion, & Tucker, 2010). Externalizing problems have been linked with smaller N200 amplitudes on no-go trials in a go/no-go task (Moadab et al., 2010; Troller-Renfree, Zeanah, Nelson, & Fox, 2018; Woltering, Liu, Rokeach, & Tannock, 2013); however, conflicting results report both decreased and increased N200 amplitudes (Brooker et al., 2020). Given that effortful control, which develops by early preschool, is a precursor to later inhibitory control, it is a critical target for the identification of early risk profiles.

The late toddler and preschool age, marked by the development of effortful control (a dispositional trait reflecting the tendency to employ top-down control), denotes a shift of the anterior cingulate cortex (ACC) and prefrontal cortex (PFC) into the regulatory roles they occupy in adult cognition (Hoyniak, Petersen, Bates, & Molfese, 2018; Nigg, 2017). The rapid development of inhibitory control mechanisms begins around age 3 years (Watson & Bell, 2013) and continues through early middle childhood (5–6 years) due to both biological (brain) development and contextual experiences (Carlson, 2005). Accordingly, study of inhibitory control during this period can provide a look at developing mechanisms and presage the later emergence of regulatory dysfunction. Notably, as contextual experiences in the environment influence inhibitory control, this is also a potential target for preventative intervention (Baker, Liu, & Huang, 2020).

The current focus of early intervention research is during the transitory period from childhood to adolescence, when the emergence of initial symptoms of schizophrenia-spectrum disorders occurs (Costello et al., 2011) because rapid brain development co-occurs with substantial role changes, hormonal changes and, commonly, exposure to additional stressors. Development of brain regions associated with emotion and reward processing early in adolescence is related to the increased sensitivity to emotional and social experiences observed during this period (Dumontheil, 2016). Extant research in the psychosis risk literature focuses on adolescence (e.g., Fryer et al., 2019) or uses retrospective methods (e.g., examining home video recordings; Walker, 1990) with individuals already showing clinical or subclinical symptoms of psychosis in the interest of developing and implementing early interventions (Fusar-Poli, McGorry, & Kane, 2017; McGorry, Hartmann, et al., 2018).

However, limited research has been conducted connecting early childhood, when mechanisms giving rise to inhibitory control are rapidly developing, with emerging symptoms in adolescence (Ashford, Smit, van Lier, Cuijpers, & Koot, 2008). The premorbid period of psychosis has been particularly neglected in research, though there are observable

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pre-symptomatic differences in children who later develop psychotic disorders in areas such as attachment (Blair, Nitzburg, DeRosse, & Karlsgodt, 2018) and motor abnormalities (Osborne et al., 2020; Walker, 1990). One exception to the retrospective focus is a single study which prospectively examined emotional and behavioral problems at ages 3 and 6 years and found associations with PLEs reported at age 10 (Bolhuis et al., 2018). No research is known to have linked early inhibitory control and electrophysiology to later PLEs.

In contrast, substantial prospective research has been conducted on internalizing (e.g., Hentges et al., 2020; Liu et al., 2018; Sætren et al., 2021) and externalizing symptoms (e.g., Buss et al., 2014; Hentges et al., 2020; Quistberg & Mueller, 2020). This research demonstrates that many types of psychopathology share risk factors (i.e., childhood adversity, trauma; Ashford et al., 2008; Doan et al., 2012) and are associated with transdiagnostic neurodevelopmental phenotypes, most notably irritability (Damme, Norton, Briggs-Gowan, Wakschlag, & Mittal, 2022; Klein, Dougherty, Kessel, Silver, & Carlson, 2021; Wakschlag et al., 2019). In prior work from this sample, electrophysiology has been examined as related to irritability, indicating that higher irritability scores are linked with poor task performance and increased conflict monitoring (Deveney et al., 2019). Additional longitudinal research on early predictors of psychopathology risk, particularly with long-term follow-up, is essential and can aid in the identification of both general and specific risk factors for different types of serious mental illness (Costello et al., 2011; Goschke, 2014; MacNeill et al., 2021).

The current study prospectively examines the relationship between neurocognitive task performance in early childhood as related to later psychotic-like experience scores (PLEs) in early adolescence at long-term follow-up. PLEs occur within the general population, yet higher levels indicate an increased vulnerability to developing psychotic disorders (Kelleher & Cannon, 2011). To the authors' knowledge, this is the first paper including prospective longitudinal brain:behavior prediction of PLEs. Utilizing tasks collected at the pre-school wave measuring cognitive functions impaired in schizophrenia-spectrum disorders (Gotra et al., 2020; Groom et al., 2008), we aim to identify risk markers for psychosis which are differentiable from pluripotent risk factors for psychopathology and which may inform probabilistic models of risk. An identifiable risk profile for psychosis in early childhood would improve the understanding of psychopathological mechanisms and introduce novel approaches to early identification and prevention prior to the emergence of symptoms of schizophrenia-spectrum disorders.

To do this, accuracy on a developmentally appropriate go/no-go task is examined for precursors to inhibitory control deficits seen in schizophrenia-spectrum disorders. In a complementary analysis, focusing on a subsample of children who participated in the same longitudinal time points but received the inhibitory task paired with an electrophysiology paradigm, we sought to determine whether preschool-aged N200 waves, a biomarker of inhibitory function, replicated the behavioral findings. The additional physiological measure provides conceptual confirmation of behavioral results and can add additional clues about rapidly developing mechanisms underlying inhibitory control. While examining

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these questions, we also interrogate specificity by including internalizing and externalizing symptom outcomes.

Methods

Participants

Participants included in the current analyses represented a sub-sample of the Multidimensional Assessment of Preschoolers Study (MAPS) sample who returned for long-term follow-up, pre-adolescent (ages 8–12) assessments. The MAPS study is a longitudinal study following participants from pre-school age (ages 3–5) through the transition to adolescence and enriched for psychopathology risk by oversampling for irritability and exposure to violence at initial recruitment (see Briggs-Gowan et al., 2019; Wakschlag et al., 2015).Initially, 425 pre-school aged children were well-characterized through a series of developmentally-appropriate, lab-based tasks including EEG. Three hundred ten children attempted the go/no-go task, 93 of whom had concurrent EEG data (see Deveney et al., 2019 for detail). The current study focuses on the 107 participants with pre-school wave behavioral data on the go/no-go task, pre-adolescent wave data on internalizing symptoms, externalizing symptoms, and transition to adolescence wave PLEs (see Supplementary Figure 1). This analytic sample did not differ from those who attempted the task in terms of gender, poverty status, or racial background. Poverty status was assessed by meeting at least one of two criteria: the poverty threshold from the 2010 census based on family's income and household size or receipt of Temporary Assistance for Needy Family (TANF) services. The current study is the first to publish results from the early adolescent wave PLEs.

Of these 107 participants, there were 34 participants who had usable ERP data for the go/no-go task. Information about the age, race, sex, socioeconomic status, and clinical symptom scores for each of these groups is in Table 1. The group of participants with ERP data were significantly older than participants in only the behavioral sample, $t(105)=-2.921$, $p=.004$, and had higher accuracy on the go trials in block 2, $t(79.641)=-2.220$, $p=.029$. These differences are expectable given that children able to tolerate ERP data collection are often older and/or better able to tolerate frustration (Brooker et al., 2020). There were no other significant differences between the groups.

Clinical Outcomes

Assessment of internalizing/externalizing symptoms and PLEs were conducted across two waves during the transition to adolescence. (1) the pre-adolescent wave of the study when participants ranged from age 8 to age 11 and (2) during the "tween" wave when participants ranged from age 9 to age 12. Assessment of internalizing and externalizing symptomatology was obtained during the pre-adolescent wave through parent interviews using the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition version of the Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version (K-SADS-PL; Kaufman, Birmaher, Brent, Ryan, & Rao, 2000). The number of clinically relevant symptoms present within internalizing (major depressive and separation anxiety) and externalizing (oppositional defiant, conduct, and attentional deficit hyperactivity) domains were summed to create internalizing and externalizing symptom scores.

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During the “tween” wave, youth participants completed a brief 7-item questionnaire about PLEs. This questionnaire, the Adolescent Psychotic-like Symptom Screener/Community Assessment of Psychic Experiences (APSS-CAPE; Dolphin, Dooley, & Fitzgerald, 2015; Kelleher & Cannon, 2011; Kelleher, Harley, Murtagh, & Cannon, 2011) asks participants the frequency at which they experience several common types of PLEs. Frequency was rated never, sometimes, often, or nearly always and converted to a number 1–4. For the current study, frequency scores for each of the items were summed and this total score was used. Internal consistency for the APSS-CAPE was good with Cronbach’s Alpha at α=.81.

Neurocognitive Tasks

Go/No-Go Task—The go/no-go task completed at the pre-school wave was a developmentally-appropriate task called the “Whack-A-Mole Task” (WAM) based on the task developed by Sarah Getz and the Sackler Institute for Developmental Psychobiology (https://www.sacklerinstitute.org/cornell/assays_and_tools/WackAMole/mole_agree). The task was modified with IRB permission to include a frustration manipulation in the second of three blocks (Deveney et al., 2019; Lamm & Lewis, 2010; Lewis & Stieben, 2004; Stieben et al., 2007). In this task, children helped Mr. Farmer save the vegetables in his garden by pressing a button to “whack” the moles (go trials; 140 trials/block) and avoid pressing a button when an eggplant appeared (no-go trials; 60 trials/block). The first block began with 40 go trials to build up a prepotent response. Participants had 1,500 ms to respond and received feedback in the form of a red and yellow flashing image which appeared following commission errors (button press on no-go trials) and omission errors (no button press after 1,500 ms on go trials). See Figure 1A.

During the non-frustration (first and third; A & C) blocks, the interstimulus (ISI) interval ranged from 1,600 to 2,200 ms and participants received positive feedback every 40 trials, regardless of performance, in the form of a happy Mr. Farmer surrounded by eggplants. Following these blocks, participants were told that they saved Mr. Farmer’s vegetables and received a puzzle piece used to earn a prize from the treasure box at the end of the session. During the frustration (second; B) block, the ISI was shortened to 1,500–1,900 ms to promote errors and after every 40 trials, participants were presented with negative feedback, regardless of performance, in the form of a sad Mr. Farmer surrounded by moles. Following this block, participants were told that they did not save Mr. Farmer’s vegetables and would not win a puzzle piece. All children won a prize at the end of the session.

ERP Acquisition and Processing

EEG data collected during the go/no-go task was collected using a SynAmp RT amplifier (Neuroscan) and a 32-channel Ag/AgCl Quick cap (Neuroscan; electrodes: FP1, FP2, F7, F3, Fz, F4, F8, FT7, FC3, FCz, FC4, FT8, T7, C3, Cz, C4, T8, TP7, CP3, CPz, CP4, TP8, P7, P3, Pz, P4, P8). Ag/AgCl electrodes placed above and below the left eye and bilaterally on the outer canthi were used to collect the vertical and horizontal electrooculogram, respectively. Data were referenced to the right mastoid during recording, digitized at 1,000 Hz, and filtered using a 100 Hz low-pass filter. Impedances were kept below 10 kΩ. EEG data were re-referenced offline to the averaged mastoids and filtered using an FIR zero-phase shift low-pass 40 Hz filter. Automatic artifact rejection removed any data with

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amplitudes ±100 μV, and a regression procedure was used to remove eyeblinks (Semlitsch, Anderer, Schuster, & Presslich, 1986). Artifact-free data were segmented into 1,200 ms epochs with 200 ms pre-stimulus onset used for baseline correction. Data were averaged separately by trial type within each block and trials with incorrect behavioral responses were excluded. For go trials, participants had a minimum of 69 trials with a range of 319 and standard deviation of 86.0. For no-go trials, participants had a minimum of 26 trials with a range of 133 and a standard deviation of 36.8.

The N200 component was quantified as the mean amplitude between 300 and 500 ms averaged across frontocentral sites (F3, Fz, F4, FC3, FCz, FC4), based on previous literature in related tasks and populations (Grabell, Olson, Tardif, Thompson, & Gehring, 2017; Lewis, Lamm, Segalowitz, Stieben, & Zelazo, 2006; Stieben et al., 2007) and inspection of grand average waveforms. Across these, the mean amplitudes for each site for go trials were: −3.42, −3.90, −2.15, −1.78, −2.76, −3.40; mean amplitudes for no-go trials were: −4.37, −4.86, −4.37, −2.80, −3.71, −3.47. The N200 component was maximal at Fz. As has been found with young children (Ciesielski, Harris, & Cofer, 2004; Johnstone, Pleffer, Barry, Clarke, & Smith, 2005; Jonkman, 2006), the N200 component occurred later than is typical for older children and adults. There were no significant differences in latency between trial type or significant correlations between latency and PLE or symptom scores.

Analytical Strategy

To examine whether performance on the go/no-go task at pre-school age was related to subsequent PLEs, accuracy for each trial type in the three task blocks were added to a repeated measures ANCOVA as dependent variables. Covariates in the model were the total PLE score and internalizing and externalizing symptom scores. This analysis allows for the clinical outcomes data to remain continuous, providing additional information about the severity of subclinical signs of emerging psychopathology. Including internalizing and externalizing symptom data served as foils to determine the specificity to PLEs.

A complementary analysis was conducted with the subsample of participants with ERP data. Because N200 amplitude is hypothesized to be related to response inhibition (Deveney et al., 2019), individuals' N200 mean amplitudes were compared across go and no-go trial types for each block. Total PLE score and internalizing and externalizing symptom scores were added as covariates.

Results

Symptom Scores

Pearson's correlations were performed between symptom scores to determine whether the symptom types co-varied. There was no significant correlation between PLE score and internalizing, $r(105)=.006$, $p=.954$, or externalizing symptoms, $r(105)=-.039$, $p=.690$. Internalizing and externalizing symptoms were positively correlated, $r(105)=.570$, $p<.001$.

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Go/No-Go Task Behavioral Performance

A repeated measures ANCOVA with factors of block and trial type found a significant effect of total PLE score, meaning that pre-school age behavioral task accuracy (percent of trials correct) predicted early adolescent PLEs, $F(1,101)=4.038$, $p=.047$, $\eta_p^2=.036$. As expected, there was also a significant interaction such that average accuracy in pre-school was lower on no-go trials than on go trials for individuals who later had a higher PLE score, indicating a specific deficit in inhibitory control rather than a general performance deficit, $F(1,101)=3.976$, $p=.049$, $\eta_p^2=.041$. There was no significant interaction between total internalizing symptom score and trial type, $F(1,101)=0.008$, $p=.931$, $\eta_p^2=.003$, or total externalizing symptom score and trial type, $F(1,101)=0.006$, $p=.686$, $\eta_p^2=.001$, which suggests this specific deficit predicts only later PLE scores. Lower accuracy during the frustration block compared to non-frustration blocks predicted later internalizing, $F(2,202)=5.618$, $p=.004$, $\eta_p^2=.058$, and externalizing symptoms, $F(2,202)=4.663$, $p=.010$, $\eta_p^2=.045$, but not later PLE scores, $F(2,202)=1.093$, $p=.337$, $\eta_p^2=.011$. Lower overall accuracy approached significance in predicting later internalizing symptoms, $F(1,101)=3.814$, $p=.054$, $\eta_p^2=.033$. There were no other significant relationships. See Figure 1B. Results did not notably differ when age, gender, or poverty status were included in the model.

Go/No-go Task Event Related Potentials

For the subset of the sample with ERP data, a repeated measures ANCOVA with factors of block and trial type, covariates of total PLE score, internalizing, and externalizing symptom scores, and dependent variable of mean N200 amplitude was conducted. Consistent with previous literature linking higher N200 amplitude with higher inhibitory control, there was a significant main effect of trial type, such that the mean N200 amplitude was higher for no-go trials than for go trials, $F(1,30)=5.570$, $p=.025$, $\eta_p^2=.144$. This indicates that mechanisms underlying inhibitory control were more active on no-go trials, which require inhibitory control, than on go trials, which do not. As expected, having smaller N200 amplitudes on no-go trials than on go trials predicted higher PLE scores, $F(1,30)=6.075$, $p=.020$, $\eta_p^2=.100$. Smaller N200 amplitudes across trial type predicted later internalizing symptoms at a trend level, $F(1,30)=3.567$, $p=.069$, $\eta_p^2=.080$. Additionally, a larger difference in N200 amplitude between go and no-go trials predicted later externalizing symptoms at a trend level, $F(1,30)=3.404$, $p=.075$, $\eta_p^2=.059$. No other significant relationships were observed. See Figure 2 for the grand average waveform and supplementary figures 2 and 3 for the grand average waveform of participants who did and did not report PLEs, respectively. Results did not notably differ when age, gender, or poverty status were included in the model.

Discussion

The present study examined whether early childhood brain:behavior patterns of inhibitory control performance (assessed with a behavioral go/no-go task and concurrent ERP measures) predicted emerging psychosis symptoms measured by PLE scores in the “tween” period (ages 9–12), a time when the first signs of schizophrenia-spectrum disorders emerge. We found meaningful predictive and parallel patterns at behavioral and neural levels. Lower

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behavioral accuracy on only no-go trials was associated with higher levels of participant-reported PLEs. This pattern was specific to PLEs and, in contrast, results indicated that lower behavioral accuracy in the preschool age predicted higher levels of internalizing and externalizing symptoms in pre-adolescence. Complementing the behavioral results, amplitude of the N200 component on no-go trials (indexing inhibitory control) was related to the level of PLEs, with higher PLEs associated with smaller N200 amplitudes. Taken together, these results suggest that distinct behavioral and electrophysiological profiles identified in early childhood which related to PLEs at the transition to adolescence may provide important and conceptually-relevant information about neurodevelopmental vulnerability to psychosis far earlier than previously demonstrated (Mittal & Wakschlag, 2017).

Participants with higher PLE scores at age 9–12 achieved comparable accuracy during pre-school on the go trials to their low PLE peers; however, individuals with higher PLE scores had significantly lower accuracy on no-go trials when compared with participants with lower PLE scores. This difference highlights a specific deficit in inhibitory control which does not extend to overall performance, and is consistent with inhibitory control deficits in schizophrenia-spectrum disorders (Doege et al., 2010; Mittal et al., 2016). Higher PLE scores were also associated with smaller mean N200 amplitudes on no-go trials, indicating a decrease in inhibitory control indexed by electrophysiology. This is consistent with predictions and behavioral results and may provide insight into mechanisms behind early inhibitory control deficits and risk for PLEs. Additionally, the brain:behavior patterns strengthen inference with both behavioral and physiological methods aligning. These results lend support to developmental models of psychosis risk (Cougnard et al., 2007; Rajkumar, 2014) because disruptions in early childhood reflect similar patterns to later psychopathology and predict later PLE scores. Additionally, these findings indicate a potential early childhood marker of risk for schizophrenia-spectrum disorders which is discriminable from general risk for psychopathology, and a potential target for intervention (Baker et al., 2020; Pietto et al., 2018) if inhibitory control deficits increase risk itself (Abramovitch, Short, & Schweiger, 2021). Further prospective longitudinal research with interview-based measures of psychotic symptomatology is necessary, including follow-up of those with elevated vulnerability to psychosis (i.e., high PLEs) through the risk period for developing schizophrenia. Some existing large, neurodevelopmental cohorts include both measures of inhibitory control and of PLEs or psychotic symptoms (e.g., Philadelphia Neurodevelopmental Cohort, Adolescent Brain and Cognitive Development) which provide the opportunity to replicate and extend the current findings in large samples. Additionally, incorporating psychosis outcome measures into further large neurodevelopmental cohort studies such as the HEALthy Brain and Child Development Study (HBCD) can provide additional information about markers of risk for psychosis in early childhood and inform preventative intervention efforts.

Interestingly, neither internalizing symptoms nor externalizing symptoms were linked with a specific deficit of inhibitory control. Both types of symptoms were behaviorally linked with lower overall performance under emotion induction conditions. However, there was no interaction between trial types indicating that, in contrast with PLEs, both types of trial demonstrated similar decrements in performance. Electrophysiological results indicated that

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lower N200 amplitude was related with higher internalizing symptom scores at a trend level, consistent with the mixed results found in previous studies (Hum et al., 2013; Moadab et al., 2010). Higher externalizing symptom scores were predicted by N200 amplitudes at a trend level, with N200 amplitudes being higher on no-go trials than on go trials and a larger difference observed for those with higher externalizing symptom scores. Critically, these results support the finding of a specific deficit in inhibitory control that predicts later PLE scores but not later internalizing or externalizing symptoms.

Existing theories of developmental models of probabilistic risk for developing schizophrenia-spectrum disorders often conceptualize risk as progressive deviation from normative developmental trajectories (Insel, 2010; Rajkumar, 2014). However, research has demonstrated the importance of genetic, pre-natal, perinatal, and early life influences (Blair et al., 2018; Davies et al., 2018; Kelleher & Cannon, 2011; MacNeill et al., 2021; Owen, Craddock, & Jablensky, 2007; Vargas & Mittal, 2022) in impacting risk for schizophrenia-spectrum disorders. The present study suggests that not only are these factors present early in life but also that they can be identified at both behavioral and neural levels. A more accurate representation of developmental models of risk for psychopathology may indicate that individuals with higher risk are not only deviating from normative developmental trajectories but also starting from a different neural position. For example, reduced interneuron activity in adolescent development (Insel, 2010) may be confounded by starting at lower level of activity. Presuming that, as seen in the current study, it is possible to observe early differences indicative of different developmental trajectories, it follows that early intervention in early childhood (during the premorbid period) may interrupt the projected course of non-normative development.

The current study has several limitations. First, the lack of repeated measures of inhibitory control prevents an examination of developmental trajectories. Future research in this area could enhance understanding about the relationship between early inhibitory control deficits and later inhibitory control as well as a more nuanced conceptualization of the relationship between the development of inhibitory control and the emergence of psychopathology. Second, a smaller subsample with ERP data limits the ability to draw definitive conclusions about the relationship between an early index of inhibitory control and later psychopathology. Additional research with a larger sample size could confirm and elaborate on this relationship, including examining earlier waveforms indexing attention that may contribute to the observed effects. We also were not able to control for preschool age symptoms, though the prevalence of symptoms such as PLEs in this early period is likely rare (and difficult to assess with reliability and validity). This study examines only early symptoms which could be indicative of risk for disorders without the determination of final diagnoses for the participants in this sample. As such, the current analysis only discusses the relative degree of observed risk for psychosis and does not examine the presence or absence of psychopathology meeting diagnostic thresholds. We also measured PLEs with a brief survey as opposed to interview-based measures which, although far less resource intensive, may result in modestly inflated scores if normative experiences are also captured. Finally, negative symptoms are more closely related to inhibitory control deficits in schizophrenia. As a result, the current study may underestimate effects by using PLEs rather than subclinical signs of negative symptoms; however, methods of measuring these

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subclinical negative signs are currently less refined than those measuring positive symptom-like experiences such as PLEs.

Conclusions

The current study advances efforts in early identification of psychosis risk substantially, by prospectively linking for the first time both behavioral and neural markers at preschool age to PLEs experienced at 9–12. This analysis strengthens and modifies neurodevelopmental models for psychosis which extend into the premorbid period (Insel, 2010; Mittal & Wakschlag, 2017). By moving prediction of risk earlier, it may be possible to prevent the developmental cascade leading to the onset of psychotic symptoms instead of intervening in the adolescent and young adult periods (McGorry, Ratheesh, & O'Donoghue, 2018). Additional research in the premorbid period for psychosis is imperative for a fuller understanding of the neurodevelopmental mechanisms and potential targets for intervention during these early developmental stages.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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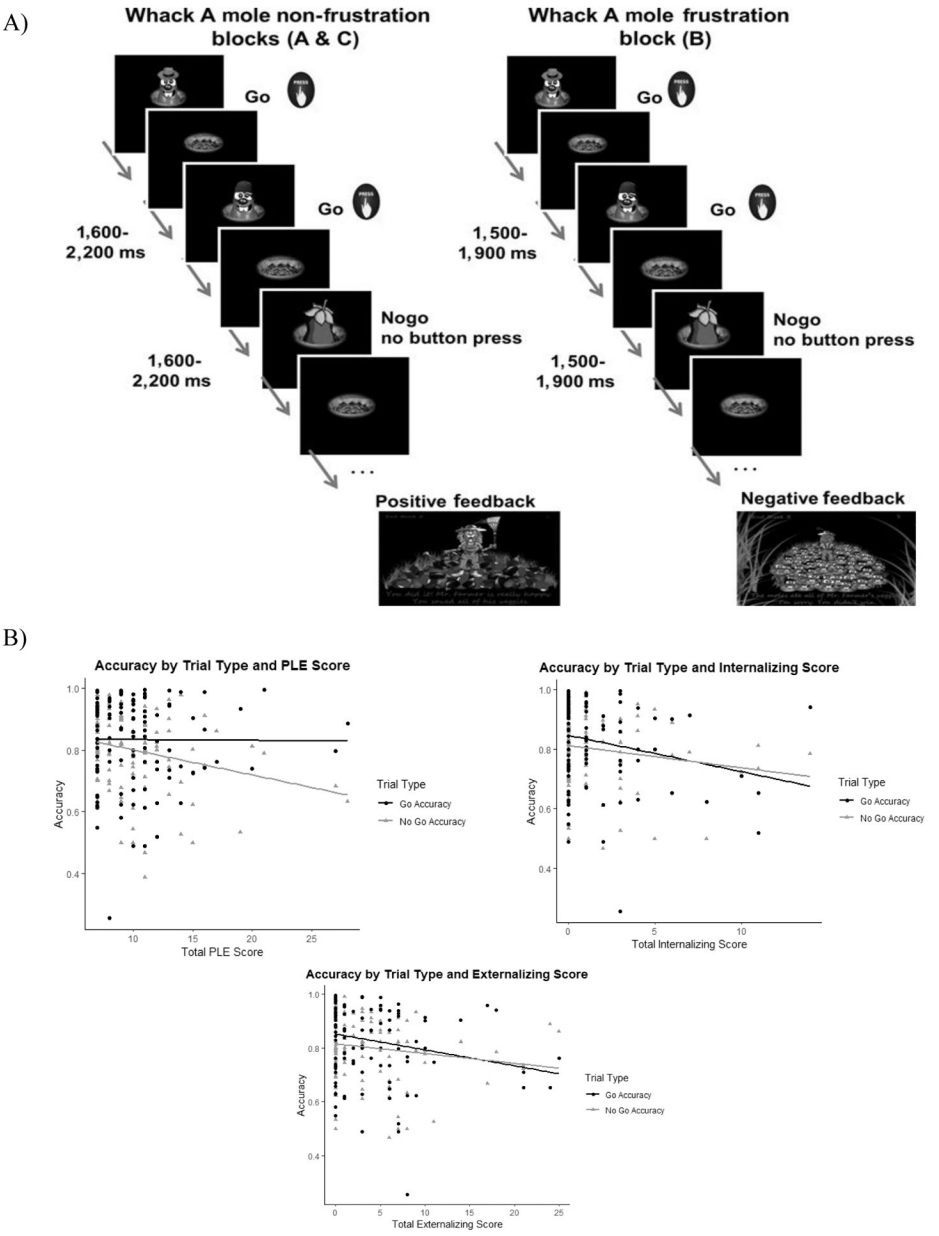

Figure 1.

A) Depiction of experiment protocol from Deveney et al., 2019. Go and No-go trials are indicated by the mole or eggplant, respectively. Blocks A and C always resulted in positive feedback. Block B had shorter response windows to promote errors and induce frustration, and was always followed by negative feedback. B) Scatterplots of the correlation between accuracy on Go and No-go trials and later Internalizing Symptoms Score, Externalizing Symptoms Score, and Psychotic-Like Experiences Score.

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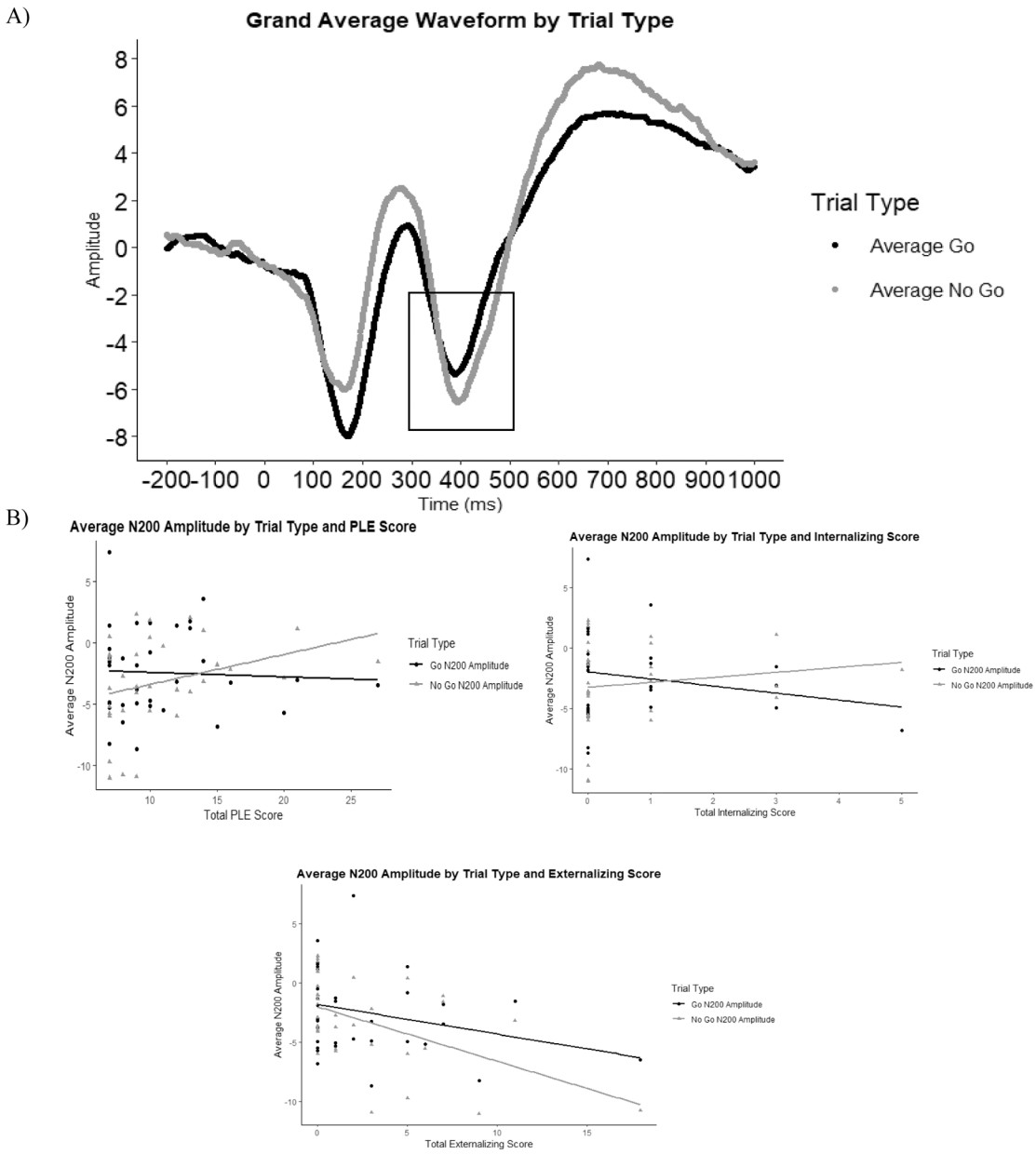

Figure 2.

A) Grand average waveform for Go and No-go trials. Negative amplitudes are plotted down. Box indicates the N200 waveform used in analyses. B) Average N200 amplitudes for Go and No-go trials correlated with later Internalizing Symptoms Score, Externalizing Symptoms Score, and Psychotic-Like Experiences Score.

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Table 1.

Demographic information for the full behavioral sample and the subsample of participants with ERP data. An asterisk indicates a significant difference between the two groups at $p = .004$.

Demographics		
	Behavioral Sample	**ERP Subsample**
	Number	
Sex (female)	58 (54%)	22 (64%)
Total Participants	107	34
	Age in years (SD)	
Mean Baseline Age	4.47 (.64)*	4.72 (.56)*
Mean Pre-adolescence Age	8.72 (.70)	8.94 (.75)
Mean Tween Age	11.50 (.68)	11.78 (.60)
	SES	
Poor	42	13
Near-Poor	11	3
Not Poor	54	18
	Race/Ethnicity	
African American	57	16
Hispanic	33	13
Caucasian	17	5
	Clinical Scores (Mean (SD))	
Psychotic-Like Experiences	10.27 (3.84)	10.79 (4.66)
Internalizing Symptoms	1.22 (2.31)	.64 (1.19)
Externalizing Symptoms	3.63 (5.38)	2.65 (4.03)