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Post-error adjustment among children aged 7 years with a familial high-risk of schizophrenia or bipolar disorder – A population-based cohort study

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Short title: Error adaptation in children of parents with SZ or BP
Abstract

The cognitive control system matures gradually with age and shows age-related sex differences. To gain knowledge concerning error adaptation in familial high-risk groups, investigating error adaptation among the offspring of parents with severe mental disorders is important and may contribute to the understanding of cognitive functioning in at-risk individuals. We identified an observational cohort through Danish registries and measured error adaptation using an Eriksen Flanker paradigm. We tested 497 7-year-old children with a familial high-risk of schizophrenia (n=192) or bipolar disorder (n=116) for deficits in error adaptation compared with a control group (n=189). We investigated whether error adaptation differed between high-risk groups compared with controls and sex-differences in the adaptation to errors, irrespective of high-risk status. Overall, children exhibited post-error slowing, but the slowing of responses did not translate to significant improvements in accuracy. No differences were detected between either high-risk groups compared with controls. Boys showed less post-error slowing and post-error slowing after incongruent trials than girls. Our results suggest familial high-risk of severe mental disorders does not influence error adaptation at this early stage of cognitive control development. Error adaptation behavior at age 7 years shows specific sex differences.

Keywords: post-error slowing, post-error improvement of accuracy, error adaptation, schizophrenia, bipolar disorder.
**Introduction**

Schizophrenia and bipolar disorder are severe and complex neurodevelopmental disorders (Murray & Lewis, 1987; Weinberger, 1987) and among the most costly and debilitating disorders for the affected individuals, their relatives and the broader society. As early signs of schizophrenia and bipolar disorder are rare in the general population, studies of enriched populations, such as children with familial high-risk of these disorders provide insight into disease processes and disease development over time. Children with a familial high-risk of schizophrenia show several impaired cognitive functions, such as lower intelligence (Agnew-Blais & Seidman, 2013; Hemager et al., 2018; Sugranyes et al., 2017), poorer working memory (de la Serna et al., 2017; Hemager et al., 2018), attention deficits (Agnew-Blais & Seidman, 2013; Burton et al., 2018; Cornblatt, Obuchowski, Roberts, Pollack & Erlenmeyer-Kimling, 1999; Hemager et al., 2018; Hemager et al., 2019) beyond subtle deficits in interference control (Burton et al., 2018). Studies among children with a familial high-risk of bipolar disorder, on the other hand, show inconsistent results in relation to intelligence (Bora & Özerdem, 2017; de la Serna et al., 2017; Hemager et al., 2018; Sugranyes et al., 2017) attention, visual and verbal memory, processing speed, except for consistent deficits in working memory (Bora & Özerdem, 2017; Hemager et al., 2018; Hemager et al., 2019) and deficits in cognitive flexibility (Burton et al., 2018; Patino et al., 2013). Finally, children with a familial high-risk of schizophrenia exhibit motor impairments (Burton et al., 2016), and high prevalence of ADHD (Ellersgaard et al., 2018), whereas this was not evident for children with FHR-BP (Burton et al., 2017; Duffy, 2012; Ellersgaard et al., 2018).

A central part of children’s development including extending their cognitive, motor, and emotional capacities entails learning from their mistakes by adapting their behavior to prevent future mistakes. Behavioral adaptation to situational demands is fundamental to daily functioning across the lifespan (Diamond, 2013; Ullsperger, 2006; Ullsperger, Danielmeier & Jocham, 2014) and reflects a central
part of our cognitive control processes. Specifically, error adaptation, is the ability to adapt behavior after an erroneous response by slowing response speed in a subsequent trial to improve accuracy, and avoid additional errors (Rabbitt, 1966; Ullsperger, Harsay, Wessel & Ridderinkhof, 2010). This change in response speed is called post-error slowing (PES). PES may reflect the ability to assert cognitive control and is viewed as a marker of adaptation (Rabbitt, 1968). This adaptation process may lead to improved accuracy in post-error trials compared with post-correct trials. The improved accuracy as a consequence of post-error adjustments is called post-error improvement of accuracy (PIA) (Danielmeier & Ullsperger, 2011; Marco-Pallares, Camara, Munte & Rodriguez-Fornells, 2008).

Cognitive control develops relatively slowly and is not fully mature until early adulthood (Cragg, 2016; Tamnes, Walhovd, Torstveit, Sells & Fjell, 2013). This development depends on the maturation of various structures including the anterior cingulate cortex (ACC) and the dorsolateral prefrontal cortex (PFC). (Niendam et al., 2012; Tamnes, Walhovd, Torstveit, Sells & Fjell, 2013). Electrophysiologically, erroneous responses elicit error-related negativity (ERN), which is a neurocognitive marker that reflects ACC activity and cognitive control processes (Taylor, Stern & Gehring, 2007; van Veen & Carter, 2006). These processes are believed to lead to compensatory behavioral changes such as PES (Ladouceur, Dahl & Carter, 2007). The literature indicates that the ERN amplitude becomes larger with age from childhood to adulthood suggesting continued maturation of the neural system for cognitive control (Ladouceur, Dahl & Carter, 2007; Tamnes, Walhovd, Torstveit, Sells & Fjell, 2013; van Meel, Heslenfeld, Rommelse, Oosterlaan & Sergeant, 2012).

Brain maturation follows slightly different trajectories in girls and in boys and is influenced by chromosomes, gonadal steroid hormones, cultural and environmental factors (Giedd, Castellanos, Rajakase, Vaituzis & Rapoport, 1997; Gogos, Ney, Seymour, Van Rheefer & Felmingham, 2019;
Age-related sex differences during development have also been documented in relation to the ERN amplitude from childhood to adulthood, with girls having a distinct development pattern from boys (including an earlier increase in ERN amplitude than boys) (Davies, Segalowitz & Gavin, 2004). Furthermore, among adults, males showed increased ERN amplitude relative to females (Larson, South & Clayson, 2011) and females showed more pronounced PES at the behavioral level than males (Fischer, Danielmeier, Villringer, Klein & Ullsperger, 2016). To our knowledge, this issue has not been examined in a large sample of children before puberty.

Cognitive control is crucial for educational achievement, social and psychological development, and mental and physical health (Diamond, 2013). Individuals with schizophrenia and their unaffected first-degree relatives display deficits of cognitive control and altered ACC and PFC connectivity during response inhibition tasks (Sambataro et al., 2013). Children of parents with either schizophrenia or bipolar disorder have an increased risk for developing psychiatric disorders in adulthood (Rasic, Hajek, Alda & Uher, 2014) and associated cognitive problems. Therefore, investigating cognitive control is important to establish and identify both cognitive with-in person resilience factors or vulnerabilities, which may contribute to understand the cognitive functioning in at-risk individuals. To our knowledge no studies have assessed PES or PIA in children with a familial high-risk of schizophrenia or bipolar disorder.

The overarching purpose of this study was to assess behavioral markers of error adaptation in a large sample of children with a familial high-risk of schizophrenia (FHR-SZ) or bipolar disorder (FHR-BP) within a narrow age range. We hypothesized that children with FHR-SZ or FHR-BP would make more errors and exhibit less PES and PIA compared with controls during a task requiring cognitive control. We also hypothesized that boys would exhibit less error adaptation than girls irrespective of familial high-risk status.
Material and methods

The Danish Data Protection Agency approved the study protocol and we received permission to draw data from registers from the Danish Ministry of Health. The Danish National Committee on Health Research Ethics evaluated the protocol, but because of the absence of any intervention, ethical approval was not regarded necessary by the authority. Participating parents and legal guardians gave written informed consent.

Study design and participants

The Danish High Risk and Resilience Study - VIA7 is a prospective and population-based cohort established in Denmark between January 1, 2013 and January 31, 2016 (Thorup et al., 2015) and consists of 522 Danish children aged 7 years with either no, one, or two parents diagnosed with schizophrenia spectrum psychosis or bipolar disorder. The cohort was constructed using The Danish Civil Registration System (DCRS) (Pedersen, Gotzsche, Moller & Mortensen, 2006) to identify children born and living in Denmark who turned 7 years during the study period in combination with The Danish Psychiatric Central Research Register (DPCR) (Mors, Perto & Mortensen, 2011). The DPCR consists of diagnosis of in- and out-patient contact and allowed identification of biological parent diagnosed with either schizophrenia spectrum psychosis defined as schizophrenia, delusional disorder, or schizoaffective disorder (ICD 10-codes: F20, F22 and F25 or ICD 8-codes: 295, 297, 298.29, 298.39, 298.89, 298.99) or bipolar disorder (defined as ICD 10-code F30, F31 or ICD 8-codes 296.19 or 296.39). Control children (population-based children of parents with no diagnoses of schizophrenia spectrum disorder or bipolar disorder) were matched to children with FHR-SZ based on sex, age and municipality. Children with FHR-BP were included as a non-matched group.
**Procedure**

All raters were blinded to group affiliation throughout the examination and analyses. In the present study, we assessed error adaptation using a modified Eriksen flanker task. Furthermore, we used the total standard scores from the Movement Assessment Battery for Children - second edition (Henderson, Sugden & Barnett, 2007) as an estimate of motor function (published in detail elsewhere (Burton et al., 2017)) to assess the impact of motor function in error adaptation. Moreover, we used a modified version of the ADHD-Rating Scale (DuPaul, Power & Anastopoulos, 1998; Makransky & Bilenberg, 2014) to assess symptoms of attention-deficits/hyperactivity disorder (ADHD) rated by primary caregivers (described in detail elsewhere (Ellersgaard et al., 2018)) and investigated their relation to error adaptation. Current level of functioning of the child was evaluated using the Children’s Global Assessment Scale (CGAS) (Shaffer et al., 1983).

**Eriksen Flanker Task**

The Eriksen Flanker Task (Eriksen & Eriksen, 1974) is a visuospatial task involving an interference effect, which we used in a modified version implemented in E-prime 2 (Psychology Software Tools, 2012). A short training session preceded the actual flanker task. The child was instructed to fixate on a dot presented in the center of a computer screen for 800 ms. Trials started with six horizontal flanker arrows appearing below fixation. After 100 ms a central target arrow appeared pointing either in the same direction as the flanker arrows in congruent trials (<<<< << <<, >>> > >>>) or in the opposite direction in incongruent trials (<<<< > << <<, >>> < >>>) (Figure 1). The child was instructed to respond to the direction of the central arrow as quickly and accurately as possible with either a left or a right mouse button click. The target- and flanker-arrows remained on the screen until a response was registered. Trials were terminated by the response and were immediately followed by 800-ms fixation screen of the next trial (the response-stimulus-interval, RSI), leading to
a response-target interval (RTI) of \((800 \text{ ms} + 100 \text{ ms}) = 900 \text{ ms}\). The intertrial-interval (ITI) is the time from the end of one trial to the beginning of the next trial (Compton, Heaton & Ozer, 2017). Since trials in this flanker task finish with the response, the RSI is equal to ITI=800 ms.

The flanker task consisted of 400 trials divided into two blocks of 200 trials separated by a short break. The overall probability of congruent and incongruent trials and left and right responses, was held at 0.5, respectively. The occurrence of each trial type was pseudo-randomized separately for each child. An exclamation mark represented performance feedback and appeared when responses were erroneous or slower than an adaptive individual threshold value (i.e., the continuously updated mean response time plus 1.5 standard deviations) (Burton et al., 2018; Eichele et al., 2017). After a correct response a fixation dot was shown on the screen until the beginning of the next trial. The RSI after correct and non-correct responses were the same.

Outcome Measures for Flanker task

PES was assessed from consecutive sequences of four trials (a CCEC trial sequence) consisting of an error trial (E), the two correct trials directly preceding the error trial (\(C_{E-1}\) and \(C_{E-2}\), respectively) and a correct post-error trial (\(C_{E+1}\)) to avoid contamination by global fluctuations in performance during the experiment, such as time-on-task changes in motivation or response caution (Dutilh et al., 2012). Correspondingly, we calculated PES robust = Mean RT post-error (\(C_{E+1}\)) – Mean RT pre-error, post correct trials (\(C_{E-1}\)), as suggested by a previous study (Dutilh et al., 2012). A minimum of five CCEC sequences per participant was required to calculate a meaningful PES \(n = 3\) of the
controls were excluded. PES for each subject was used in the overall mean of PES of all the participants from FHR-SZ, FHR-BP or controls. Outliers were removed before the assessment of PES. Firstly, trials with reaction time less than 200 ms and greater than 10,000 ms were removed. Thereafter trials were discarded with reaction time exceeding 3 SD from the mean. Reaction times are reported elsewhere (Burton et al., 2018).

Post-error accuracy was calculated as the average accuracy on all post-error trials (except trials 1 and 201 where no preceding trial was available). Post-error improvement of accuracy (PIA) was calculated by subtracting post-correct accuracy from post-error accuracy and is expected to be positive if reflecting cognitive adaptation and adjusted behavior. Error rates were calculated as 1 - accuracy for congruent trials and incongruent trials, respectively. The calculation of PES and PIA ignores whether errors occurred on congruent or incongruent trials. Therefore, PES and PIA were also assessed in follow-up analyses, where PES and PIA were calculated solely based on trials following incongruent trials. We refer to the slowing after an error in an incongruent trial as “post-error slowing after incongruent trials (PES_{incongruent})” and the improvement in accuracy as “post-error improvement in accuracy after incongruent trials (PIA_{incongruent})”. A minimum of five CCEC sequences per participant were required to calculate a meaningful PES_{incongruent} which resulted in n=20 exclusions (n=7 from the controls, n=7 from the FHR-BP and n=6 from the FHR-SZ group).

**Statistical Analysis**

For the a priori hypothesis, the error adaptation measures (PES, PIA, PES_{incongruent} and PIA_{incongruent}) were tested by assessing the effect of group in a mixed-model analysis with a random effect of matched set (including singleton cases). The model was adjusted for age and sex. In addition to these independent variables, we considered all three-way, and two-way interactions of group, sex and age. Statistically nonsignificant interaction terms were eliminated via backward stepwise regression, with the constraint that the model at each step had to be hierarchically well-formulated.
All lower-order terms such as sex, age and group were included in the model regardless of statistical significance.

We explored the following intermediate variables in the mixed model: error rate for incongruent trials, ADHD symptoms (rated by caregiver ADHD-Rating Scale) (Ellersgaard et al., 2018) and motor function (measured with the Movement Assessment Battery for Children – second edition, total standard score) (Burton et al., 2017) in which PES and PIA, respectively, served as the dependent variable.

Variables with a skewed distribution were logarithmically transformed (log 2) before analysis, and the results were backward transformed with antilogarithm. For the outcome variable error rate, we used the same mixed model and expanded the model with an unstructured covariance matrix, describing variance and correlation between the two outcomes for each child (congruent and incongruent). Covariates included age, sex and condition (congruent or incongruent). We explored the intermediate variables ADHD symptoms and motor function in the repeated mixed-model in which error rate served as the dependent variable.

The relationship between the PIA and PES (Danielmeier & Ullsperger, 2011) was assessed by a Pearson correlation as well as the relationship between PES and CGAS, measuring children’s current level of functioning. We considered $p$-values < .05 as significant. All statistical analyses were conducted in SAS software (version 9.4).

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Table 1 here

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Results
Our cohort consisted of 522 children aged 7 years. A total of 500 children completed the Flanker task of which 497 children had a minimum of five consecutive sequences of trials around errors, required to calculate a meaningful PES.

We assessed 192 (38.6%) children of parents with schizophrenia, 116 children (23.3%) of parents with bipolar disorder and 189 (38.0%) children with parents without schizophrenia or bipolar disorder (Table 1). On group level, children exhibited PES and PES_incongruent irrespective of familial high-risk groups (cf. Table 2). The test for fixed effects of PES revealed a significant effect of sex \((F(1,492) = 5.17, p = .024)\), but no differences across groups \((F(2,492) = 0.30, p = .743)\) or across age \((F(1,492) = 1.12, p = .291)\). No interactions were significant (Table 2). The post-hoc test showed that boys displayed less prominent PES compared with girls (mean difference -56.4, 95% CI: [-105.2; -7.64], \(p = .024\)) (Figure 2). In the mixed-model, a high error rate for incongruent trials lead to a significantly smaller PES (estimate -65.49, 95% [-86.48; -44.50], \(p < .0001\)). The influence of ADHD symptoms was not significant (estimate -1.59, 95% [-4.40; 1.23], \(p = .27\)) nor was the effect of motor function (estimate 6.00, 95% [-1.76; 13.76], \(p = .13\)) on PES (Table 3). There was no relevant correlation between the child’s current level of functioning (CGAS) and PES in the overall sample (Pearson correlation \(r = -.03 p = .51\)), nor for the different high-risk groups (FHR-SZ: \(r = -.03, p = .66\); FHR-BP: \(r = -.026, p = .78\); and controls: \(r = -.064, p = .39\)).

Table 2 and Figure 2 here

Some children exhibited post-error improvement in accuracy (PIA), but none of the three groups on average displayed PIA (Table 2). Accordingly, PIA did not differ across groups \((F(2,350) = 0.10, p = .902)\), with age \((F(1,464) = 0.18, p = .673)\) or sex \((F(1,294) = 0.59, p = .445)\) and none of the 2-way or 3-
way interactions were significant. A better motor function lead to a larger PIA (estimate 0.003, 95% [0.0008; 0.0058], \(p = .01\)). ADHD symptoms had no effect on PIA (estimate -0.0005, 95% [-0.001; 0.0004], \(p = .29\)) (Table 3). The correlation between PES and PIA was significant for children in the control group (Pearson correlation \(r = 0.1998, p = .0058\)) (Figure 3), but not for children in the FHR-SZ (\(r = .066, p = .37\)) or FHR-BP (\(r = -.077, p = .41\)) groups.

Follow-up analyses showed that the test for fixed effects of post-error slowing after incongruent trials, \(\text{PES}_{\text{incongruent}}\) revealed no effect across groups \((F_{(2,473)} = 0.25, p = .78)\), but significant effect of sex \((F_{(1,473)} = 4.00, p = .046)\), age \((F_{(1,473)} = 4.15, p = .042)\) and the significant interaction age-by-group \((F_{(2,473)} = 4.75, p = .0091)\). Boys exhibited less \(\text{PES}_{\text{incongruent}}\) compared with girls (mean difference -58.62, 95% CI: [-116.2; -1.036]) \(p = .046\) (Figure 2B). The age-by-group interaction showed how \(\text{PES}_{\text{incongruent}}\) increased with age for both the FHR-BP and FHR-SZ groups but not for the control group.

The test for fixed effects of post-error improvement in accuracy after incongruent trials \((\text{PIA}_{\text{incongruent}})\) showed no significant differences across groups \((F_{(2,335)} = 1.66, p = .19)\), sex \((F_{(1,269)} = .53, p = .47)\) or age \((F_{(1,432)} = 0.37, p = .55)\). None of the 2-way or 3-way interactions were significant.

Error rate differed between sexes, boys made 25% more errors than girls (estimated ratio 1.25, 95% [1.093; 1.430], \(p = .0012\)). Error rate was clearly affected by congruency, children exhibited 59.5% less errors in the congruent trials compared with the incongruent trials (estimated ratio 0.405, 95%
[0.382; 0.430], \( p < .0001 \)). No effects of error rate across familial high-risk groups \( (F_{(2,492)} = 1.24, p = .29) \) or age \( (F_{(1,492)} = 2.11, p = .15) \) were present. A higher level of ADHD symptoms significantly increased error rate by 1.3\%, (estimated ratio 1.013, CI 95\% [1.005; 1.020], \( p = .0012 \)), whereas a higher level of motor function significantly reduced error rate by 6\% (estimated ratio 0.94, CI 95\% [0.921; 0.960], \( p < .0001 \)) (Table 3).

Discussion

This large population-based cohort study showed that at age 7 years, children exhibited error adaptation in the form of PES. However, slowing of responses did not translate to improvements in accuracy (PIA). Familial high-risk status did not differentially affect PES or PES_{incongruent}; however, the significant ‘age-by-high-risk-group interaction’ in relation to PES_{incongruent} showed how PES_{incongruent} increased with age for both the FHR-BP and FHR-SZ groups but not for the control group. Boys generally displayed less error adaptation than girls in relation to PES and PES_{incongruent}. We detected a negative relationship between PES and error rate, with lower PES associated with higher error rates. Motor function and ADHD symptoms did not influence PES. Although we detected no group or sex differences in relation to PIA, better motor function lead to a larger PIA. Moreover, the two measures of error adaptation (PES and PIA) were significantly correlated for children in the control group, but not for children in the FHR-SZ or FHR-BP groups. No relationship between ADHD symptoms and PIA was identified. The error rate did not differ by familial high-risk status, but was influenced by congruency, sex, ADHD symptoms, and motor ability. Specifically, children exhibited more errors in incongruent trials and boys demonstrated
more errors than girls across all groups. Furthermore, a higher level of ADHD symptoms increased error rates, whereas better motor function significantly reduced error rates.

Although error adaptation is not fully matured at age 7 years, our findings suggested that post-error adjustment behavior may be influenced by sex at this stage of development. Furthermore, our results indicated that the familial high-risk for severe mental disorders at this stage of cognitive control development did not significantly affect error adaptation, but the lack of correlation between PIA and PES for the familial high-risk groups was noteworthy.

Error adaptation has been measured in individuals with schizophrenia and bipolar disorder, but few studies have tested error adaptation in offspring (Patino et al., 2013). Therefore, our study provided new knowledge regarding behavioral error adaptation in a large sample of children with a familial high-risk for severe mental disorders at primary school age. We found that children displayed PES at this age, but there was no difference in PES between the groups. Related literature concerning adults diagnosed with schizophrenia is inconclusive (Abrahamse et al., 2016), with reports of absent or reduced PES (Alain, McNeely, He, Christensen & West, 2002; Carter, MacDonald, Ross & Stenger, 2001; Kerns et al., 2005) as well as intact PES (Laurens, Ngan, Bates, Kiehl & Liddle, 2003; Mathalon et al., 2002; Perez et al., 2012; Polli et al., 2006). Furthermore, to our knowledge, the only available study that tested PES in individuals with bipolar disorder found no difference in PES from controls (Saunders, Goodwin & Rogers, 2016). Together with these studies, our study contributes to the discussion of error adaptation as an endophenotype reflecting the underlying vulnerabilities in the neurodevelopmental process of developing severe mental illness. Thus, PES and PIA do not appear to fulfill the criteria for an endophenotype at this development stage. The immaturity was not specific to FHR-SZ or FHR-BP groups as PES was present in all three groups and PIA in none. However, the relative immaturity in all three groups may prevents us from detecting the high-risk group-based differences that we expect to emerge at an older age.
(Reichenberg et al., 2010). As such, it is possible that different trajectories may be revealed because of later maturation. Follow-up studies into adolescence are necessary to provide knowledge of the development of error adaptation in the vulnerable group of children born with a familial high-risk of severe mental disorders.

Brain maturation through childhood into adulthood may display sex differences (Kaczkurkin, Raznahan & Satterthwaite, 2019), which may derive from different neurodevelopmental trajectories (Giedd, Raznahan, Mills & Lenroot, 2012; Lenroot et al., 2007; Ruigrok et al., 2014) or possibly as a result of the more pronounced brain structure variability among males compared with females (Wierenga, Sexton, Laake, Giedd & Tamnes, 2018). These sex differences in the developing brain may contribute to differences in cognitive performance (Grabowska, 2017; Gur et al., 1999). Our behavioral results showed there were sex-based differences in PES at age 7 years whereby boys displayed less PES than girls, although there was no sex difference in relation to PIA. These findings were consistent with those from adult studies, which reported men displayed less PES than women (Fischer, Danielmeier, Villringer, Klein & Ullsperger, 2016; Thakkar et al., 2014) but no sex effects in PIA (Fischer, Danielmeier, Villringer, Klein & Ullsperger, 2016). Furthermore, we detected a sex difference in relation to errors, as boys made more errors than girls. These findings may indicate that at this age, boys may not learn as much from their errors or adapt their behavior as appropriately as girls. Our behavioral finding of a sex difference may reflect different brain maturation at the age of 7 years between boys and girls in relation to errors and error adaptation.

Currently, no consensus has been reached as to the mechanisms underlying PES (Notebaert et al., 2009; Purcell & Kiani, 2016; Ullsperger & Danielmeier, 2016), how to measure PES, and which intertrial interval (ITI) (Compton, Heaton & Ozer, 2017) or response-stimulus-interval (RSI) (Danielmeier & Ullsperger, 2011; Jentzsch & Dudosch, 2009) conditions are optimal for ascertaining PES. Some researchers considered PES to result from an increased motor threshold
implemented by a general motor inhibition to avoid future mistakes (Marco-Pallares, Camara, Munte & Rodriguez-Fornells, 2008). Others, interpreted PES as related to cognitive control processes associated with committing errors (Botvinick, Braver, Barch, Carter & Cohen, 2001; Plessen et al., 2015). Alternatively, PES may reflect an unspecific orientation response to uncommon or surprising events rather than the result of cognitive control (Notebaert et al., 2009). Studies also differed in the way they measured PES. Some opted to subtract the average RT on correct trials following correct trials from the average RT on correct trials following errors (Hajcak, McDonald & Simons, 2003; Kerns et al., 2004; Mathalon et al., 2002). Others chose an arguably more robust measure (Dutilh et al., 2012) in which PES was calculated based on the sequence surrounding trials with erroneous responses to avoid fluctuations in task engagement confounding PES. In addition, the duration of ITI (Compton, Heaton & Ozer, 2017) and RSI (Danielmeier & Ullsperger, 2011; Jentzsch & Dudschig, 2009) potentially play a role in ascertaining PES and how errors affect accuracy. Among adults, long ITIs lead to increased post-error accuracy, while shorter ITIs, lead to impaired post-error accuracy (Wessel, 2018). In short RSI situations, adults showed larger PES and lower post-error accuracy (Danielmeier & Ullsperger, 2011; Jentzsch & Dudschig, 2009). Furthermore, PIA has been seen at long mean ITIs (e.g., 900–2250 ms) (Danielmeier & Ullsperger, 2011; Marco-Pallares, Camara, Munte & Rodriguez-Fornells, 2008). We calculated PES with the robust measure suggested by a previous study (Dutilh et al., 2012). The ITI in our study was 800 ms, which is considered a short ITI (Compton, Heaton & Ozer, 2017). The fact that we found that children showed PES but no PIA at age 7 years could be explained by the short ITI. However, our results could also reflect the general development of the cognitive control system, as increasing PES and PIA with age has been reported in children from age 8 to 19 years (Overbye et al., 2019). This highlights the need for longitudinal developmental studies to track the emergence and changes in PES and PIA across development.
Even though PIA and PES both reflect adaptive processes, they may be caused by different underlying processes because they are not necessarily correlated and do not always co-occur (Danielmeier & Ullsperger, 2011). This was consistent with our findings that 7-year-old children exhibited PES but not PIA at the group level, even though some children in all three groups exhibited PIA. However, we only found a significant positive correlation between PES and PIA for the control group, indicating higher PES was associated with higher PIA (although PIA remained negative for most children). For children in the control group with a positive PIA, PES was reached between 0 and 500 ms (see the upper right quadrant of Figure 3), whereas for the majority of control group children with a negative PIA, PES was between −500 ms and + 500 ms (Figure 3). No correlation between PIA and PES was established for children in the FHR-SZ and FHR-BP groups, indicating different associations between PIA and PES in these familial high-risk groups.

PES was calculated using a pre-post measure to remove the effects of global performance shifts as suggested by (Dutilh et al., 2012). Because the pre-post method is not applicable to PIA, PIA was calculated using a standard procedure which allows post-error adaptation to be confounded with changes in motivation, error rate etc. across the experiment. However, this might be the reason why the correlation between PES and PIA is observed only for the control group. Perhaps, PIA in the high-risk groups is more strongly driven by global performance shifts (e.g. motivation or response caution decrease during the trial, as the child get tired, which result in more errors and inaccurate responses), thus reducing the common variance with (control-related) PES.

One study documented a positive correlation between PIA and PES in children and adolescents (Overbye et al., 2019), whereas studies of adults either showed no correlation between PIA and PES (Carp & Compton, 2009; Danielmeier & Ullsperger, 2011) or confirmed a relationship (Hajcak, McDonald & Simons, 2003). The prolonged maturation of the cognitive control system means it is
unclear if our behavioral error adaptation data reflected immature cognitive control processes or an automatic orienting response. Further studies during development are needed to clarify this point.

A higher rate of errors is commonly reported among individuals with ADHD (Balogh & Czobor, 2016; Van De Voorde, Roeyers & Wiersema, 2010), which was consistent with our finding that a higher level of ADHD symptoms increased error rates. A meta-analysis of 1667 patients with ADHD with a broad age range including adults with a mature cognitive control system (age range 6–41 years, mean age 12.2±7.9 years) documented a diminished PES in patients with ADHD as a group compared with controls (Balogh & Czobor, 2016). In contrast to our expectations, we could not replicate that ADHD symptoms significantly influenced PES or PIA at age 7 years in our sample of 497 children. These results could reflect the immaturity of their cognitive control system.

Brain imaging studies have documented involvement of the cerebellum, posterior parietal cortex and primary motor cortex in error adaptation in addition to the ACC (Desmurget et al., 2001). Our results showed that better motor function significantly reduced error rates. Moreover, our results suggested that better motor function improved the ability to display PIA, whereas motor function did not influence PES. These findings indicated involvement of different brain areas and processes in error adaptation.

Our study had major strengths, including the novelty of assessing error adaptation in a large, same-aged pre-pubertal sample with a familial high-risk of severe mental disorders. In addition, we assessed motor function and ADHD symptoms in the same children, which allowed us to investigate the impact of these parameters in relation to error adaptation. The present Eriksen Flanker Task provided performance feedback after errors. This implies that post-error adaptation does not solely rely on internal error detection (as in typical ERN studies) but could also rely on feedback processing. This somewhat limits the interpretation of the results and could include a
potential explanation to why no significant differences between groups were found. A further limitation of our study was that cognitive control was only assessed using a behavioral task. Future studies would benefit from assessing these abilities using brain imaging and electrophysiology to gain a more profound understanding of the neural underpinnings and development of cognitive control before puberty.

Conclusions

At age 7 years, children exhibit PES and PES\textsubscript{incongruent}, but the slowing of responses does not translate to improvements in accuracy. Although we found no differences in PES, PIA or error rate in the FHR-SZ or FHR-BP group compared with the control group, PES and PES\textsubscript{incongruent} showed sex related differences with boys displaying less error adaptation than girls. We detected a correlation between PES and PIA for children in the control group, but not for children in the familial high-risk groups. We detected a negative relationship between PES and error rate, with lower PES associated with higher error rates. Error rates were influenced by sex, congruency, ADHD symptoms and motor ability. Our findings suggest that error adaptation behavior at age 7 years displays specific sex differences at this stage of development. Furthermore, our results indicate that familial disposition of severe mental disorders at this stage of cognitive control development does not influence error adaptation except for the differential relationship between PIA and PES.

References


Figure legends:

Figure 1: The Eriksen Flanker Task design and trial sequence. The child was instructed to fixate a dot presented in the center of a computer screen for 800 ms. Trials started with six horizontal flanker arrows. After 100 ms a central target arrow appeared either as congruent trials or as incongruent trials. The target- and flanker-arrows remained on the screen until a response was registered. Trials were terminated by the response and were immediately followed by 800-ms fixation screen of the next trial. The response-stimulus-interval (RSI) is equal to the intertrial-interval (ITI) since trials in this flanker task design finish with the response.

Figure 2: Results of The Eriksen Flanker Task. (A) Means of post-error slowing after congruent and incongruent trials (PES) and (B) means of post-error slowing after incongruent trials only (PES_{incongruent}) for boys (blue squares) and girls (red circles) between children with a familial high-risk of schizophrenia (FHR-SZ), children with a familial high-risk of bipolar disorder (FHR-BP) and control subjects. Error bars indicate 95% confidence interval.

Figure 3: Association between post-error slowing (PES) and post-error improvement of accuracy (PIA) for children in the control group (n=189). PES on the X-axis is measured in milliseconds and PIA on the Y-axis is measured in percent.