Atypical attentional filtering of visual information in youth with chromosome 22q11.2 deletion syndrome as indexed by event-related potentials

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ABSTRACT

Background: Youth with chromosome 22q11.2 deletion syndrome (22q) face one of the highest genetic risk factors for the development of schizophrenia. Previous research suggests impairments in attentional control and potential interactions with elevated anxiety and reduced adaptive functioning may increase the risk for developing psychosis in this population. Here, we examined how variations in attentional control relate to the presence or severity of psychosis-proneness symptoms in these individuals.
Methods: To achieve this, we measured attentional control in youth (12–18 years) with 22q (N = 35) compared to a typically developing group (N = 45), using a flanker task (the Distractor Target task) while measuring neural activity with event-related potentials.
Results: Similar to previous findings observed in people with schizophrenia, greater attentional capture by, and reduced suppression of, non-target flanker stimuli characterized participants with 22q and was indexed by the N2pc (N2-posterior-contralateral) and P_D (distractor positivity) components. Although we observed no relationships between these components and measures of psychosis-proneness in youth with 22q, these individuals endorsed a relatively low incidence of positive symptoms overall.
Conclusions: Our results provide neural evidence of an attentional control impairment in youth with 22q that suggests these individuals experience sustained attentional focus on irrelevant information and reduced suppression of distracting stimuli in their environment. Impairments in attentional control might be a valid biomarker of the potential to develop attenuated positive symptoms or frank psychosis in high-risk individuals long before the age at which such symptoms typically arise. The evaluation of such a hypothesis, and the preventive potential for the putative biomarker, should be the focus of future studies.

1. Introduction

Chromosome 22q11.2 deletion syndrome (22q) is a condition affecting 1 in every 2000–3000 live births (Grati et al., 2015; Kobrynski and Sullivan, 2007; Shprintzen, 2008). It appears to significantly increase the risk of developing schizophrenia (Bassett and Chow, 2008; Drew et al., 2011; Green et al., 2009), placing the microdeletion among the strongest genetic risk factors for this disorder. Recent reports suggest lower rates of frank psychosis than first thought (Schneider et al., 2014)

and so the true psychosis incidence and the factors that affect it remain under investigation.

Attentional control impairments have been reported in youth with 22q and may form part of the risk profile for the development of schizophrenia in this population. These impairments have been evidenced using the Attentional Network Test (Fan et al., 2002), which consists of a spatial cueing task (Posner, 1980) and a flanker task (Eriksen and Eriksen, 1974) to examine orienting, alerting and executive control networks. Using the ANT, children with 22q have shown

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difficulties adjusting their attentional focus to inhibit the processing of irrelevant stimuli, and have shown difficulties disengaging their attention from inappropriately-cued locations, compared to typically-developing (TD) children (Bish et al., 2005; Sobin et al., 2004; Stoddard et al., 2011). Recent work has also reported a consistent deficit in sustained attention that occurs throughout childhood, adolescence, and adulthood in people with 22q, with the greatest deficit observed in adults with a psychotic disorder (Morrison et al., 2020). Similar attentional control impairments have been documented extensively in people with schizophrenia across multiple domains relative to healthy control groups, as measured with Stroop, AX-CPT, and antisaccade tasks (Bansal et al., 2021; Cohen et al., 1999; Galaverna et al., 2012; Manoach et al., 2002; McDowell et al., 2002; Radant et al., 2007; Sereno and Holzman, 1995; Westerhausen et al., 2011). Since these attention impairments are recognized as a core feature of schizophrenia, their presence may index increased risk for the development of schizophrenia in youth with 22q. However, attentional control consists of multiple sub-processes, and these processes are still not well characterized in the 22q population. A better understanding of attentional control mechanisms in youth with 22q may therefore aid early psychosis detection, prevention, and treatment.

Recently, researchers have proposed a hyperfocusing hypothesis to explain attentional control impairments in people with schizophrenia (Luck et al., 2019; 2014) which may be extended to youth with 22q. According to this hypothesis, people with schizophrenia concentrate their attention processing resources more intensely and more narrowly than healthy control participants – even when this approach is counterproductive to task goals. Evidence for this hypothesis comes from behavioral and EEG visual search studies showing people with schizophrenia exhibited greater attentional capture by non-target distractor stimuli that partly matched task goals (e.g., when a distractor matched the target color participants were looking for, Luck et al., 2014; Mayer et al., 2012; Sawaki et al., 2017). Additional support for this hypothesis comes from studies showing that people with schizophrenia can focus their attention on one location and withdraw attention from others successfully, but struggle to distribute their attention broadly when the task demands it (Hahn et al., 2016; 2013; 2012).

Evidence suggests hyperfocusing may be characteristic of people with 22q. Specifically, in addition to impairments in attentional control that are observed behaviorally (Bish et al., 2005; Sobin et al., 2004; Stoddard et al., 2011), anxiety is one of the most common psychiatric symptoms observed in people with 22q (Angkustsiri et al., 2012; Feinstein et al., 2002; Green et al., 2009; Tang et al., 2014), which may impact how their attentional resources are allocated during stressful situations. According to attentional control theory (Derakshan and Eysenck, 2009; Eysenck et al., 2007; Eysenck and Derakshan, 2011), elevated anxiety can lead to impairments when inhibiting attention in response to distracting stimuli and when allocating attention to task-relevant stimuli, consistent with the results of previous work using the ANT test in children with 22q (Bish et al., 2005; Sobin et al., 2004; Stoddard et al., 2011). Our research has also shown that greater anxiety was associated with lower adaptive functioning in children with 22q (Angkustsiri et al., 2012) which suggests anxiety negatively impacts their day-to-day life. Taken together, elevated anxiety may disrupt attentional control processes in youth with 22q, which may contribute to their increased risk for the development of schizophrenia. This is speculative, as there is no direct evidence that anxiety mediates the development of later symptoms of schizophrenia. However, longitudinal work has shown that the presence of an anxiety disorder at baseline significantly predicted the presence of a psychotic disorder in people with 22q (Gothelf et al., 2013). Furthermore, a systematic review identified that elevated anxiety was associated with the severity of psychotic symptoms such as delusions and hallucinations in people with schizophrenia (Hartley et al., 2013).

Therefore, the current study aimed to extend our understanding of attentional control mechanisms in youth with 22q, by examining the underlying neural processes via event-related potentials (ERPs) and a Distractor Target (DT) task (Sawaki et al., 2017; 2012), and examining potential associations between attentional control mechanisms and anxiety, adaptive function, and psychosis-proneness. In this task, participants are presented with a central target circle and two flanking distractor circles and are asked to monitor the central circle for a specific color (see Fig. 1) while ignoring the two flanking circles. However, one of these flanking circles occasionally matches the target color, leading to distraction. During tasks like this, Sawaki and Luck (2010) suggested that distractor stimuli (e.g., a flanking circle that matches the target color), automatically produce an "attend-to-me" signal. However, this signal can be overcome via an active top-down suppression mechanism that prevents attentional capture when the signal doesn't match task goals. Direct evidence for these processes can be measured using the N2pc (N2-posterior-contralateral) and P_D (distractor positivity) ERP components. The N2pc is a well-established, negative-going component observed within the typical N2 latency range (180–300 ms post-stimulus) at posterior electrode sites contralateral to a given stimulus that has been captured by attention (Luck and Hillyard, 1994a; 1994b). A greater N2pc is believed to reflect the focusing of attention on a target item and the filtering of nearby distractor items (Sawaki et al., 2012). The P_D is also observed within the N2 latency range but is a positive-going component observed at posterior electrode sites contralateral to a distractor item. A greater P_D is believed to reflect active attentional suppression of distractor items (Hickey et al., 2009; Sawaki et al., 2012; Sawaki and Luck, 2010). Previous studies have identified neural generators of the N2pc within both intermediate and high ventral visual processing regions, specifically area V4 and the lateral occipital cortex (Hopf et al., 2006; 2004). While the neural generators of the P_D are not yet known, it has been suggested that the P_D likely originates from the same neural source as the N2pc, as these two components have similar scalp topographies, opposite polarities, and complementary attentional processes (Sawaki and Luck, 2014).

Using the DT task, Sawaki and colleagues (Sawaki et al., 2017) found people with schizophrenia exhibited a greater N2pc response to a lateral distractor containing the target color, indicating attentional capture by the distractor. In contrast, healthy participants exhibited a greater P_D, indicating suppression of the distractor. Thus, people with schizophrenia exhibited reduced attentional control due to more attentional capture by, and less suppression of, distractors compared to healthy participants. Since these ERP components provided a neural measure of attentional control that complemented traditional behavioral measures, we chose them for the current study of youth with 22q. We measured attentional control using the DT task in youth with 22q compared with TD youth. We predicted youth with 22q would demonstrate greater attentional capture by distractor stimuli than TD youth, evidenced by task accuracy and by increased N2pc and decreased P_D ERPs. We also explored relationships between ERPs and adaptive function, anxiety, and psychosis-proneness to understand whether these factors are related to the increased incidence of psychosis in youth with 22q.

2. Methods and materials

2.1. Participants

Fifty-seven participants with 22q and 50 TD participants (12–18 years) were recruited. We excluded the data of 17 participants with 22q and 5 TD participants due to poor task accuracy (Details in *Behavioral Responses* section) and we excluded an additional five participants with 22q due to excessive ERP artifacts (Details in *EEG data processing and ERP analysis* section). This left 35 participants with 22q and 45 TD participants with both behavioral and ERP data (Table 1). Importantly, the pattern of ERP effects that was observed did not change when we excluded participants based on behavioral performance. All participants had no history of head trauma, and TD participants had no known DSM-5 Axis I disorders (American Psychiatric Association, 2013). All
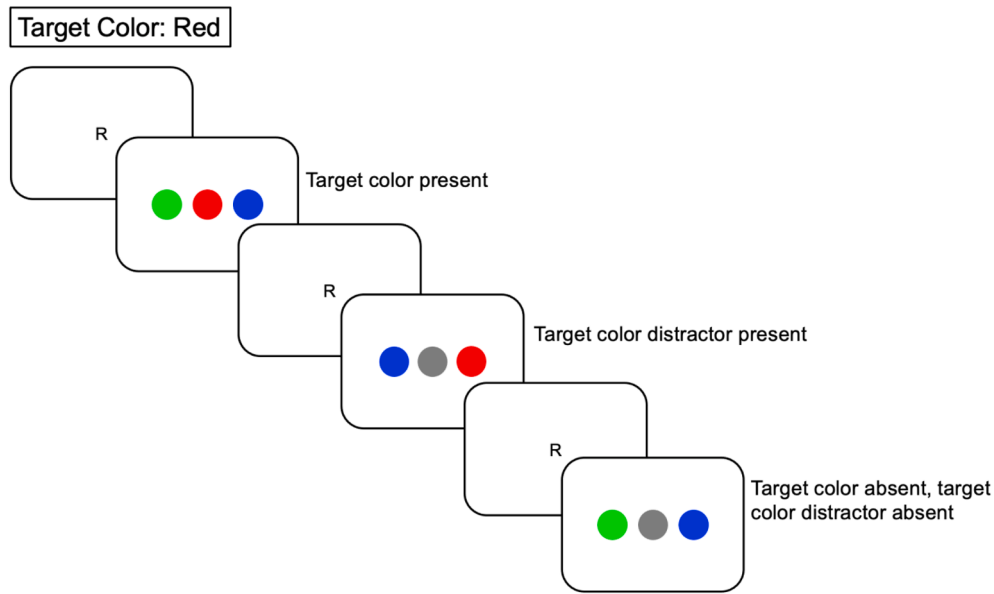
Distractor Target Task

Fig. 1. Experimental design. The DT task. Note. Participants looked for a specific target color in the center of the screen (red, blue, or green), while two colored circles flanked the target circle. Participants pressed one button if the center circle matched the target color they were looking for and pressed another button if the center circle was another color.

Table 1
Participant characteristics of final sample (mean, standard deviation).

	22q	TD
n	35	45
Age (years)	15.19, 2.43	14.97, 1.98
% Female	51.43%	55.56%
IQ (Full scale 4)***	81.94, 10.83	117.11, 13.09
IQ (Verbal)***	90.91, 9.12	115.98, 15.07

Note. No participants were taking antipsychotic medication. Groups did not differ according to age ($p = .667$) or gender ($p = .713$). ***$p < 0.001$.

participants with 22q were required to be antipsychotic medication naïve or to have previously taken them for less than one month. We assessed IQ using the Wechsler Abbreviated Scale of Intelligence (WASI-II, Wechsler, 2011) via video call before their visit, and recruited participants with a verbal IQ greater than 70 to ensure they understood the questions asked in their clinical interviews. Participants did not complete the WASI-II if their IQ was available from another reliable source in the past two years, which meant five participants with 22q provided IQ scores assessed using the Wechsler Intelligence Scale for Children-fifth edition (WISC-V, Wechsler, 2014). Differences between WASI-II and WISC-V scores were not significantly different for verbal and full-scale IQ (p's greater than 0.05), so WASI-II and WISC-V scores were aggregated in Table 1. Written informed consent from parents and verbal assent from participants was obtained before participation. This study was approved by the UC Davis Institutional Review Board and conformed to institutional and federal guidelines to ensure protection of participants (IRB Protocol no. 721614).

2.2. Stimuli and procedure

Participants were seated 57 cm from an LCD monitor (1920 × 1080) displaying a black background and tasks were presented using E-Prime version 2.0.10.353. A Logitech Precision gamepad collected behavioral responses. An actiCHamp Brain products system recorded EEG data. The EEG was filtered online with a cascaded integrator-comb antialiasing filter (half-power cutoff of 260 Hz) and digitized at 1000 Hz using

PyCorder software version 1.0.9. We fitted 32 EEG electrodes to a cap (Easy-Cap 2-C) and recorded the EEG activity reference-free. Electrodes placed above and below the right eye and adjacent to the left and right lateral canthi monitored vertical and horizontal eye movements.

2.3. DT task

On each trial, participants were presented with a horizontal array of three colored circles (see examples in Fig. 1). They were instructed to look for a specific target color in the central circle (red, blue, or green) and ignore the two colored circles flanking the target circle. Participants pressed one button if the center circle matched the target color they were looking for and pressed another button if the center circle was not the target color.

The center circle was gray (which was never a target) on 70% of trials and was red, green, or blue on the remaining 30% of trials (10% for each color). Each lateral circle was red, green, or blue on a given trial (selected independently for the two locations at random with the constraint that the two flankers were always different colors on a given trial). Each circle had a luminance of 18 cd/m^2 and subtended 1.5 degrees of visual angle. Lateral circles were presented 3.5 degrees to the left and right of the center circle (center-to-center distance). Each trial began with a variable-duration fixation letter (between 1600 and 1800 ms) presented in the center of screen to provide a fixation point and remind the participant of the target color circle they were looking for (R, B, or G). Following this, three colored circles were presented in the center of the screen for 200 ms (Fig. 1).

Participants completed 12 practice trials to ensure they understood the task, and then completed 300 experimental trials (100 with each color designated as the target). To reduce fatigue, trials were presented in six blocks of 50 pseudo-randomized trials, with each of the six blocks presented randomly, taking around 1.75 min to complete. Each of the three colors was the target for two blocks of 50 trials, so each color served as the target color in some blocks and a non-target color in others.

2.4. Outcome measures

2.4.1. Psychological assessments

Psychosis-proneness was assessed in participants with 22q using the Structured Interview for Prodromal Syndromes (SIPS, McGlashan et al., 2001). A clinician or staff member trained by T.A.N or K.B conducted interviews with the caregiver(s) of the participant first, then the participant. Questions assessed the presence of positive, negative, disorganized, and general symptoms experienced by the participant. For endorsed symptoms, the caregiver/participant elaborated on their onset, frequency, and severity. Each symptom was rated by the interviewer (0–2 does not meet criteria for attenuated psychotic symptoms; 3–5 meets criteria for attenuated psychotic symptoms; 6 meets criteria for psychotic symptoms). Ratings were discussed with T.A.N or K.B and adjusted if necessary. All participants completed the Prodromal Questionnaire – brief version (PQ-B, Loewy et al., 2011; 2005) and the Spence Children's Anxiety Scale (SCAS, Spence, 1998) child form to assess their anxiety. Participants' caregivers completed the Adaptive Behavior Assessment System (ABAS-II, Harrison and Oakland, 2003) to assess the participant's daily function, and the SCAS parent form (Spence, 1998) to assess their anxiety.

2.4.2. Behavioral responses

We analyzed 100% of DT trials to assess behavioral responses. We examined the impact of diagnosis (22q or TD) on hits and false alarms during the task. Three main trial types were analyzed: 1) Target-present i.e., trials where the center circle matched the color participants were asked to look for, 2) Target-absent: target color distractor is present i.e., trials where the center circle did not match the color participants were asked to look for, but one of the lateral circles matched the target color, and 3) Target-absent: target color distractor is absent. i.e., trials where the neither the center circle nor the lateral circles matched the color participants were asked to look for.

We averaged across trial blocks in which different colors were defined as the target, as we were not interested in differences among red, green, and blue target trials. We removed trials where RTs were under 200 ms (anticipatory responses) or exceeded 2.5 standard deviations above the individual's mean RT (attentional lapses). We excluded participants' behavioral responses if they scored less than 50% correct on over 50% of task conditions, or less than 25% correct on target trials. This removed individuals who were not engaged or did not understand the task. Following this, significantly more participants with 22q were excluded from the task (n = 17) compared to TD participants (n = 5, $p < 0.05$).

2.4.3. EEG data processing and ERP analysis

The continuous EEG signals were processed with EEGLAB (version 14.1.0b, Delorme and Makeig, 2004) and ERPLAB (version 7.0.0, Lopez-Calderon and Luck, 2014), via MATLAB (version 2017a, MathWorks). EEG data were downsampled to 500 Hz. A Butterworth bandpass filter (half-amplitude cutoffs at 0.1 and 30 Hz, 12 dB/octave) was applied to remove low-frequency drifts and high-frequency noise, and a 60 Hz notch filter removed line noise. Data were then referenced to the average of the two mastoids, and a visual inspection of the data was conducted to remove extreme muscular artifacts. We applied an independent component analysis to identify and remove components which were characteristic of eyeblinks/eye movements, which has been shown to be effective in tasks examining lateralized components such as N2pc and P_D (Drisdelle et al., 2017). Additionally, we eliminated trials containing blinks or eye movements within 200 ms of the stimulus presentation, as the participant would not have seen the stimulus. Blinks were identified using ERPLAB's blink detection tool on the uncorrected vertical eye channel, and eye movements were identified using ERPLAB's step-like artifact detection on the uncorrected horizontal eye channel.

Average ERPs were extracted from the subset of trials where the center circle was gray and one of the lateral circles matched the target color. We generated contralateral, ipsilateral, and contralateral-minus-ipsilateral waveforms relative to the location of the lateral circle that matched the target color. These waveforms were averaged across occipital and parietal electrode sites (P3/P4, P7/P8, O1/O2). At this stage, we applied an a priori exclusion rule to eliminate participants with more than 50% of trials removed due to artifacts, which meant six participants with 22q and no TD participants were excluded. For participants with 22q, significantly more artifactual trials were removed (M = 16.12%, SD = 9.08) vs TD participants (M = 11.05%, SD = 7.07, $p = 0.008$).

ERP time windows were selected for analysis by first creating one grand-averaged ERP waveform across all conditions/participants, forming a collapsed localizer (Luck and Gaspelin, 2017). Visual inspection of this grand-averaged waveform for x-axis crossings near 200 ms revealed an early negative-going N2pc from approximately 150–250 ms post-stimulus, and a positive-going PD from 250 to 370 ms post-stimulus. From this, we determined a time window of 150–370 ms was suitable to examine the balance between attentional capture and suppression of distractor stimuli indexed by the N2pc and P_D. That is, because these two components have opposite polarity, the mean voltage over the broad window will be more negative when attention to the target-matching distractor outweighs suppression and more positive when suppression outweighs attention. In this time window, the mean amplitude measured the balance between the N2pc and the P_D. We also examined the negative area under the curve for the N2pc (i.e., the area of the region defined by negative voltages) and the positive area under the curve for the P_D (i.e., the area of the region defined by positive voltages) to separately measure capture and suppression processes. We used the same time window of 150–370 ms for these area amplitude analyses.

2.5. Statistical analysis

Because the behavioral and ERP measures were non-normally distributed, Mann Whitney U tests were used in place of parametric t-tests to compare the 22q and TD groups. We examined behavioral group differences in attentional control by comparing the groups on the hit rate on Target Present trials, the false alarm rate on Target Absent (Distractor Present) trials, and the false alarm rate on Target Absent (Distractor Absent) trials. We examined ERP group differences in attentional capture and suppression indexed by the N2pc/P_D components by comparing the groups on mean amplitude (balance of N2pc and P_D), negative area under the curve (N2pc), and positive area under the curve (P_D). We also computed Spearman's correlations between ERP measures and scores from the ABAS, SCAS (parent and child forms), and SIPS. A Bonferroni correction was applied to control for multiple comparisons.

3. Results

3.1. Psychological assessments

SIPS ratings are displayed in Supplementary Table 1. Participants with 22q endorsed a relatively low incidence of positive symptoms (total positive symptom range = 0–13). Five participants with 22q (14.29%) qualified for attenuated positive symptoms, with perceptual abnormalities the most common symptom. Participants endorsed a greater range of negative symptoms (total negative symptom range = 0–20), with decreased ideational richness and avolition the most common symptoms. TD participants did not complete the SIPS, but their PQ-B scores indicated nine out of 45 (20%) scored above the total score cutoff of three or more endorsed items (highest score = six). These findings are similar to previous work (Loewy et al., 2011) that reported 13% of healthy control participants scored above the total score cutoff (highest score = seven). Participants with 22q had significantly lower adaptive functioning and greater anxiety across a range of child-reported and caregiver-reported subscales compared to TD participants

(Supplementary Tables 2-4).

3.2. DT task Behavior

Figure 2 shows DT hit rates and false alarms for participants with 22q and TD participants. Participants with 22q had a lower hit rate on Target Present trials compared to TD participants, U = 528.00, p = 0.012, effect size r = -0.28, and had a higher false alarm rate than TD participants on Target Absent (Distractor Present) trials, U = 357.50, p < 0.001, effect size r = -0.47, and on Target Absent (Distractor Absent) trials, U = 419.50, p < 0.001, effect size r = -0.40.

3.3. DT task ERPs

Figure 3 displays grand average ERP waveforms for the N2pc/P_D for both groups and mean/area amplitudes are displayed in Supplementary Table 5. In participants with 22q, the difference wave shows an N2pc and almost no P_D. This pattern appears to be followed by a second late phase of negativity that has been termed the *sustained posterior contra-lateral negativity* (SPCN) by Jolicœur and colleagues (2008), who proposed it reflects continued processing of the attended item. Overall, these 22q group waveforms suggest they tended more towards sustained capture of attention by the target-colored distractor and a lack of suppression.

In comparison, TD participants had a somewhat smaller N2pc and larger P_D and exhibited no sustained negativity, which suggests they successfully suppressed the target-colored distractor. Analyses confirmed participants with 22q exhibited a significantly greater N2pc area amplitude than TD participants, U = 493.00, p = 0.004, effect size r = -0.32. Participants with 22q also exhibited a smaller P_D relative to TD participants, U = 518.50, p = 0.009, effect size r = -0.29, and more negative mean amplitude, U = 474.00, p = 0.002, effect size r = -0.34. From these results, we suggest that although both groups initially orient similarly, the TD group suppresses their attention while the 22q group continue to focus on the flanker circles that matched the target color.

3.4. Correlations

Following the use of a Bonferroni correction to control for multiple comparisons, we observed no significant relationships between ERPs and task accuracy, anxiety, adaptive function, or psychosis-proneness scores (Supplementary Tables 6-10).

4. Discussion

This study examined differences between youth with 22q and TD youth in attentional control, a central determinant of what information is selected for deeper processing and what is ignored. We hypothesized that poorer attentional filtering in response to distracting visual information would be observed in youth with 22q relative to TD youth, and that variations in the degree of attentional filtering might relate to the presence or severity of psychosis-proneness and anxiety symptoms in the 22q population, which occur more frequently than for TD individuals. To evaluate this hypothesis, we used an adapted flanker task while task performance and brain responses were measured in youth with and without 22q, none of whom had been exposed to antipsychotic medications. This makes our sample quite unusual in the study of psychosis risk in 22q, and is also critical to obtaining the most accurate measures of cortical activity, which may be directly altered by such medications (Huhtaniska et al., 2017; Torres et al., 2013; Van Erp et al., 2018). During the task, youth with 22q were less accurate, and their ERP waveforms indicated that they failed to suppress a target-colored distractor flanker and continued to maintain their attention on this distractor. Because the two flanker colors were equally balanced in terms of being a distractor, a target, and not present, the key difference was whether the flanker colors matched the goal of detecting a specific color in the center position. In this sense, the differences between participants with 22q and TD participants reflect differences in goal-directed attention.

The results of the current study provide neural evidence of an attentional control impairment in youth with 22q compared to TD youth. Our results build on previous behavioral work that found youth with 22q struggled to dynamically adjust their attentional focus to inhibit the processing of irrelevant stimuli in the environment (Bish et al., 2005; Sobin et al., 2004) and work that demonstrated an age-related impairment in ignoring irrelevant flanker stimuli (Stoddard et al., 2011). Consistent with these studies, 7–14-year-olds with 22q have previously exhibited impairments across a range of cognitive processes involving response inhibition, cognitive flexibility, and working memory compared to their TD peers (Shapiro et al., 2014; 2013). Previously, it been difficult to isolate the specific neurocognitive processes that underlie these attentional control impairments in youth with 22q. However, our findings suggest these attentional impairments could be due, at least in part, to a tendency of youth with 22q to exhibit continued attentional focus and reduced suppression of distracting stimuli in their environment.

Our findings are consistent with the hyperfocusing hypothesis that was proposed to explain attentional control impairments in people with schizophrenia (Luck et al., 2019; 2014). Sawaki and colleagues (Sawaki et al., 2017) used the same DT task with people with schizophrenia and observed a greater N2pc and a smaller P_D in people with schizophrenia relative to healthy participants. They hypothesized that people with schizophrenia maintained a more intense representation of the task-relevant feature they needed to look for (e.g., target color). What they referred to as an aberrant hyper-focusing of attention suggests that the processing resources of people with schizophrenia are focused more intensely and more narrowly than healthy controls, due to disrupted attractor dynamics that produced an exaggerated winner-take-all type of
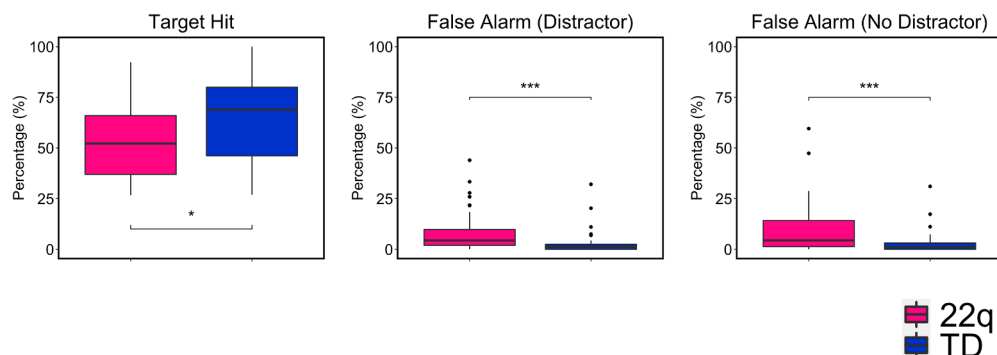

Fig. 2. DT Behavior Note. Participants with 22q were less accurate than TD participants across all trial types. ***p < 0.001, **p < 0.01, *p < 0.05.
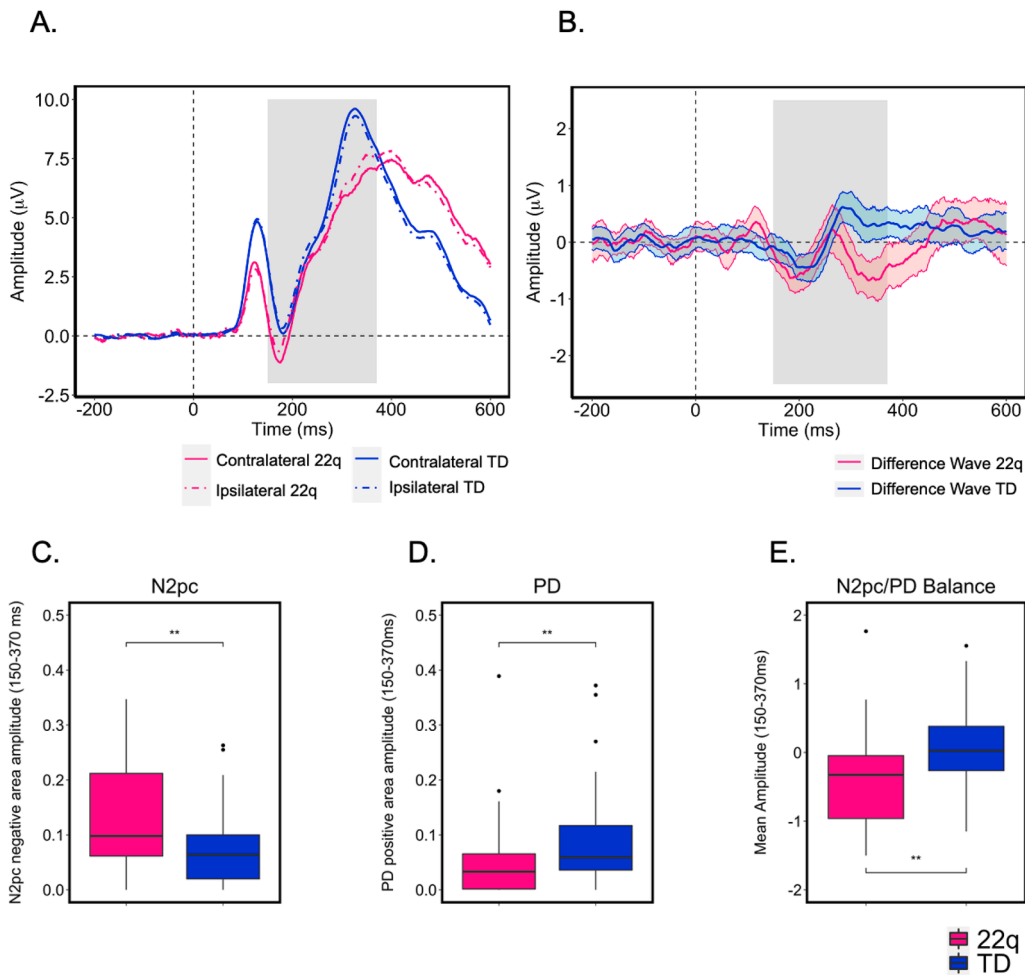
Fig. 3. DT ERPs. Note. A: Grand average ERP waveforms show the N2pc/P_D balance for participants with 22q and TD participants. B: Grand average difference waves (contralateral minus ipsilateral). The colored region around the difference waves represents 95% bootstrapped confidence intervals. C: Participants with 22q had larger N2pc area amplitudes, D: smaller P_D area amplitudes, and E: more negative mean N2pc/P_D amplitudes than TD participants. The gray shaded regions highlight the time window used to measure the N2pc and P_D effects. **$p < 0.01$.

attentional processing (Luck et al., 2014). We suggest youth with 22q exhibit a similar aberrant hyper-focusing of attention. However, given that we also observed a component resembling the SCPN in youth with 22q, which is believed to reflect continued processing of the attended item (Jolicœur et al., 2008), the impairments observed in this group may be more related to a failure to suppress their attention to distracting stimuli.

It is important to understand how attentional control impairments may relate to psychosis risk in the 22q population. We observed elevated anxiety in youth with 22q relative to TD youth, consistent with previous studies (Angkustsiri et al., 2012; Feinstein et al., 2002; Green et al., 2009; Tang et al., 2014). It has been proposed that elevated anxiety can lead to difficulties inhibiting attention to distractors and difficulties allocating attention to task-relevant stimuli (Derakshan and Eysenck, 2009; Eysenck et al., 2007; Eysenck and Derakshan, 2011). Given that we also observed reduced adaptive function and lower IQ in the 22q group, we speculate that this combination of cognitive and emotional processes may be interacting to negatively impact day-to-day functioning in this group. Because of these difficulties, anxious youth with 22q may be more likely to misattribute undue salience to the processing of stimuli that are not task-relevant (Menon and Uddin, 2010) and so these irrelevant stimuli become attractors of attention and may be difficult to suppress. This may bias their attentional selection towards atypical patterns associated with psychotic thinking.

However, we observed no significant associations between ERPs and anxiety, adaptive function, and psychosis-proneness in the 22q group. In fact, few individuals in our sample reported experiencing any psychosis-proneness symptoms. Only 14.29% of participants with 22q qualified for

attenuated positive symptoms, despite this sample being antipsychotic medication naïve. This is below current estimates of schizophrenia risk in the 22q population (25–30%, Bassett and Chow, 2008; Drew et al., 2011; Green et al., 2009), and may explain the lack of relationships between the ERPs and psychosis-proneness symptoms. These ERP effects may become more prominent among older samples where the incidence of positive symptoms is increased. If this turns out to be the case, then aberrations in attentional control indexed by the N2pc/ P_D ERPs could be a useful biomarker for risk for psychosis. Future work could test this out by repeating our study in a sample of individuals with 22q with a greater incidence of psychosis symptoms.

Although positive symptoms were minimal in this sample, over a third of participants with 22q had scores from their clinical interviews associated with decreased ideational richness, and a quarter had scores associated with increased trouble with focus and attention. High scores on these specific items have been consistently observed in previous studies using the SIPS with young people with 22q (Schneider et al., 2012; Stoddard et al., 2010; Tang et al., 2014) and may help predict the risk for later development of a psychotic disorder in this population. However, the SIPS was designed to assess the decline or loss of pre-existing functionality that occurs in the prodromal phase of psychosis. In youth with 22q, we speculate that these individuals are not experiencing a decline in pre-existing functionality. Rather, the SIPS interviews may be measuring impairments that were already part of the cognitive phenotype of developmentally delayed youth with 22q. This is evidenced by past work showing youth with 22q typically experience impairments in working memory, inhibitory control, cognitive flexibility, and lower IQ relative to their TD peers (Shapiro et al., 2014;

2013). Because of this evidence, we cannot discount the possibility that high scores on these specific symptoms may be best accounted for by developmental delay. However, future longitudinal work will enable a better understanding of whether high scores on these symptoms confer genuine risk for psychosis in youth with 22q.

We should consider our study limitations, which may be addressed by future research. First, whether the antipsychotic medication naïve nature of our sample increased the likelihood of resilience in participants with 22q, especially among older youth who were more likely to begin displaying psychotic symptoms. We recruited an anti-psychotic naïve sample because such medications can impact cortical activity (Huhtaniska et al., 2017; Torres et al., 2013; Van Erp et al., 2018). Interestingly, previous studies reported that antipsychotic treatment is uncommon in people with 22q who have endorsed psychosis symptoms (Tang et al., 2014). The reasons for this are unclear, but it suggests our sample may not deviate significantly from the general 22q community. Future work examining psychosis risk in youth with 22q whilst monitoring use of antipsychotic treatments could help to elucidate this issue. Second, we observed no relationships between ERPs and measures of anxiety, adaptive function, or psychosis-proneness, which limits our conclusions on whether these ERPs are a potential biomarker for psychosis. The lack of relationships between ERPs and psychosis-proneness could be because most participants with 22q endorsed few psychosis symptoms. However, despite the lack of significant associations between task performance or ERP indices with psychosis-proneness, our use of a cross-sectional design means we cannot rule out that attentional control impairments confer risk for the later development of schizophrenia. Presenting data from only one timepoint precludes an examination of whether the observed attentional control impairments predict risk for schizophrenia over time. Moreover, the SIPS represent a coarse examination of the presence of prodromal psychotic symptoms and were not originally designed for younger populations with intellectual impairments. This suggests there is more work to be done to provide a comprehensive understanding of psychosis risk in the 22q community. Currently, participants in this study are being recruited for a second assessment using the same DT task and measures around 2.5 years after their first assessment. We hope to use data from this second assessment to provide further insight into the relationship between attentional control impairment and psychosis risk in the 22q population. We believe the data presented in this manuscript provide a useful starting point for future investigations into developmental trajectory of psychosis risk in youth with 22q.

Third, participants with 22q had significantly lower full-scale and verbal IQ compared to TD participants. These IQ scores are consistent with previous literature showing below average IQ scores are present in most youth with 22q (De Smedt et al., 2007; Moss et al., 1999; Swillen et al., 1997). This suggests that lower IQ in people with 22q does not occur by chance, rather, lower IQ is likely an inherent characteristic of the 22q cognitive phenotype. Despite this, differences in IQ between our participants with 22q and TD participants is a key weakness of the current study. Future studies may benefit from including matched IQ samples or utilizing additional statistical techniques to specifically examine how lower IQ may relate to measures of neurocognitive function in people with 22q. Lastly, while there were minimal group differences between excluded (N = 22) and included participants with 22q (N = 35), excluded participants with 22q did have significantly lower verbal IQ than included participants with 22q. Although the task itself does not specifically tap into verbal ability, and the groups did not differ on full-scale IQ, participants need to understand the task instructions given to them by the experimenter. These participants may have had more difficulty understanding these task instructions, leading to poorer task performance and a greater rate of exclusion in this group. It is important to highlight this when considering the generalizability of our results, given the association between intellectual impairment and the later development of psychotic symptoms in those with 22q (Gothelf et al., 2007; Green et al., 2009).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2021.102877.

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