Assessing auditory processing endophenotypes associated with Schizophrenia in individuals with 22q11.2 Deletion Syndrome

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ABSTRACT

22q11.2 Deletion Syndrome (22q11.2DS) is the strongest known molecular risk factor for schizophrenia. Scalp recorded electrical brain responses to auditory stimuli have been studied extensively in schizophrenia and described as potential biomarkers of vulnerability to psychosis. Here we sought to understand whether these brain responses, along with cognitive factors associated with schizophrenia, might aid in differentiating individuals with 22q11.2DS as a function of psychotic symptoms, and ultimately serve as early signals of higher risk for schizophrenia in this population. Using a passive duration oddball paradigm and high-density electrophysiology, we tested basic auditory processing in a group of 21 adolescents and adults with 22q11.2DS with varying degrees of psychotic symptomatology and neurotypical age-matched controls. We examined whether the N1 and mismatch negativity (MMN), typically reduced in idiopathic schizophrenia, significantly correlated with psychotic symptomatology, IQ, and working memory. At the group level of analysis, individuals diagnosed with 22q11.2DS presented *increased* N1 responses and *similar* MMN responses to their neurotypical peers. Correlation analyses revealed that poorer working memory was associated with decreased MMN amplitude, and that this was largely driven by the 22q11.2DS group. We suggest that enhanced auditory sensory processing is general to 22q11.2DS, whilst poorer working memory is related to vulnerability for psychosis and smaller MMNs in 22q11.2DS.

Keywords: EEG, Auditory Evoked potential, Copy Number Variation, Event-related potential, Mismatch Negativity, Psychosis.

INTRODUCTION

22q11.2 Deletion Syndrome (22q11.2DS henceforth; also named DiGeorge syndrome or velo-cardio-facial syndrome) results from a hemizygous microdeletion of approximately 1.5 to 3 megabases on the long arm of chromosome 22. The deleted region contains about 60 known genes, some of which are highly expressed in the brain and known to affect early neuronal migration and cortical development[1, 2]. 22q11.2DS is the most common chromosomal microdeletion disorder, with prevalence estimates ranging from 1 per 1000 to 1 per 4000 live births[3, 4].

The phenotypic expression of 22q11.2DS is highly variable and ranges from severely life-threatening to less severe conditions[5]. Its clinical presentation includes variable developmental delays, cognitive deficits and neuropsychiatric conditions, and multi-organ dysfunction such as cardiac and palatal abnormalities[6, 7]. Cognitively, 22q11.2DS is characterized by deficits in executive function[8-11], nonverbal memory[12, 13], visuospatial[14-16] and visual-motor[17] processing, and working memory[18]. Approximately 60% of individuals diagnosed with 22q11.2DS meet criteria for at least one psychiatric diagnosis[19-21]—and the development of psychosis is one of the most significant concerns for parents of children with 22q11.2DS: About 30% of individuals identified with the deletion go on to develop schizophrenia[22-24]–an approximately 10-fold increase in risk compared to individuals with other developmental disabilities[25]—and more than half of adolescents with the syndrome experience schizotypical traits and transient psychotic experiences[26].

Idiopathic and 22q11.2DS-associated schizophrenia present a similar clinical path leading to psychosis[27], with subtle social deficits and poor neurocognitive performance preceding its onset both in the general population[28, 29] and in 22q11.2DS[30]. The clinical presentation of schizophrenia does not appear to differ either[31], with deficits in cognition and perception, and positive (hallucinations, delusions, thought disorder) and negative (flat affect, alogia, avolition and anhedonia) symptoms[32]. However, neurocognitive features are more severe in 22q11.2DS-associated schizophrenia, likely reflecting poorer baseline cognitive function[33]. These clinical/cognitive similarities are accompanied by high concordance of neuroanatomic correlates[34, 35 36-39], suggesting that common cerebral alterations may underlie psychotic symptomatology in both populations.

Reducing the duration of untreated psychosis, before irreversible pathological brain changes take place[40], is known to lead to better functional outcomes in patients with psychotic disorders such as schizophrenia[41, 42], strongly motivating the goal of early identification prior to frank disease onset. Since clearly observable behavioral changes are often the product of processes that have started occurring in the brain significantly earlier, the direct and reliable measurement of functional brain activity and the consequent potential to detect neural vulnerability prior to behaviorally observable symptoms is key to enabling interventions focused on prevention rather than on treatment. Sensory and cognitive auditory evoked potentials (AEP) such as the N1 and the mismatch negativity (MMN) have been identified as

potential biomarkers for vulnerability, conversion, and progression of psychosis in schizophrenia. The auditory N1 is the first prominent negative AEP[43], and reflects neural activity generated in and around primary auditory cortex[44]. Several studies demonstrate a reduction of the auditory N1 in schizophrenia, not only in chronic patients, but also in individuals at-risk for psychosis and in first-episode patients[45-49]; but see[50] for a review on contradictory evidence). The MMN occurs when a repeating stimulus (the standard) in an auditory stream is replaced by a deviant stimulus. Occurring typically 100 to 200 ms following the deviant event, the MMN is thought to reflect largely preattentive neural processes underlying detection of a pattern violation and updating of a representation of a regularity in the auditory environment[51-53]. MMN amplitude has been shown to be reduced in schizophrenia (for reviews, see[54, 55]) in at-risk individuals[56-60], recent onset[57, 58, 61-63] and chronic patients[57, 61, 64-71].

While previous studies have measured the N1 and MMN in 22q11.2DS, the limited results available have yielded inconsistent findings[72, 73]. Such inconsistencies might reflect the relatively high degree of phenotypic variability that is inherent to this population. Here, we sought to measure the relationship between auditory brain function and cognitive function, focusing on cognitive abilities known to be vulnerable in this population. We also set out to test for potential associations between MMN and N1 amplitudes and the number of psychotic symptoms expressed in the 22q11.2DS cohort. Given the working memory difficulties previously described in 22q11.2DS, stimulus onset asynchronies (SOAs) were parametrically varied to impose different levels of demand on the sensory memory system[74, 75].

METHODS

Participants

Twenty-one participants diagnosed with 22q11.2DS (age range: 14-35 years old; 12 with at least one psychotic symptom) and 21 neurotypical age-matched controls (NT) (age range: 14-38 years old) were recruited. Exclusionary criteria for the neurotypical group included hearing impairment, developmental and/or educational difficulties, neurological problems, and the presence of psychotic symptomatology. Exclusionary criteria for the 22q11.2DS group included hearing impairment and current neurological problems. Participants passed a hearing test (below 25dB HL for 500, 100, 2000, 4000Hz) performed on both ears using a *Beltone Audiometer* (Model 112). All participants signed an informed consent approved by the Institutional Review Board of the Albert Einstein College of Medicine and were monetarily compensated for their time. All aspects of the research conformed to the tenets of the Declaration of Helsinki.

Experimental Procedure and Stimuli

Testing was carried out over a 2-day period and included cognitive testing and EEG recording. IQ and working memory measures were computed from the Wechsler Adult Intelligence Scale, WAIS-IV[76] or the Wechsler Intelligence Scale for Children, WISC-V[77]. To quantify the number of psychotic symptoms, either the Structured Clinical Interview for DSM-5, SCID-V[78] or the Structured Clinical Interview for DSM-IV Childhood Diagnoses, Kid-SCID[79] was performed.

The EEG protocol focused on auditory processing, utilizing a duration-MMN oddball paradigm. Participants sat in a sound- and electrically-shielded booth (Industrial Acoustics Company Inc, Bronx, NY) and watched a muted movie of their choice on a laptop (Dell Latitude E6430 ATG or E5420M) while passively listening to regularly (85%) occurring standard tones interspersed with deviant tones (15%). These tones had a frequency of 1000 Hz with a rise and fall time of 10 ms, and were presented at an intensity of 75dB SPL using a pair of Etymotic insert earphones (Etymotic Research, Inc., Elk Grove Village, IL, USA). Standard tones had a duration of 100 ms while deviant tones were 180 ms in duration. These tones were presented in a random oddball configuration (excepting that at least two standards preceded a deviant) to yield an MMN. In three blocked conditions, the stimulus onset asynchrony (SOA) was either 450 ms, 900 ms or 1800 ms. Each SOA was presented in blocks of 4 minutes long, composed of 500, 250 or 125 trials respectively. Participants were presented with 14 blocks (2*450 ms, 4*900 ms and 8*1800 ms), resulting in a possible 1000 trials (and 150 deviants) per SOA.

Data acquisition and analysis

EEG data were acquired continuously at a sampling rate of 512 Hz from 64 locations using scalp electrodes mounted on an elastic cap and seven external channels (mastoids, temples, and nasion) (Active 2 system; Biosemi[tm], The Netherlands; 10-20 montage). Preprocessing was done using EEGLAB (version 14.1.1)[80] toolbox for MATLAB (version 2017a; MathWorks, Natick, MA). Data were downsampled to 256 Hz, re-referenced to TP8 and filtered using a 1 Hz high pass filter (0.5 Hz transition bandwidth, filter order 1690) and a 45 Hz low pass filter (5 Hz transition bandwidth, filter order 152). Both were zero-phase Hamming windowed sinc FIR filters. Bad channels were automatically detected based on kurtosis measures and rejected after visual confirmation. Artifacts were removed by running an Independent Component Analysis (ICA) to exclude components accounting for motor artifacts, eye blinks and saccades and bad channels. After ICA, the excluded channels were interpolated, using the spherical spline method. Data were segmented into epochs of -100ms to 400ms using a baseline of -100ms to 0ms. These epochs went through an artifact detection algorithm (moving window peak-to-peak threshold at 120 µV). No significant differences were found between number of trials included in the analyses per group (22q11.2DS group: average trial rejection = 5.36%; NT group: average trial rejection = 3.30%; t = -1.08, df = 35.12, p = .29).

The definition of the N1 and the MMN windows was based on the typical time of occurrence of the N1 and duration-MMN components, and on visual confirmation that amplitudes were maximal in these intervals. N1 amplitude was measured between 80 and 120 ms. The MMN is the difference between deviants and standards and was here measured between 200 and 240 ms (100 to 140 ms post deviance onset). Amplitude measures were taken at FCz, where signal was maximal for both groups. For the correlation analyses, a composite measure of the response was used to reduce the number of tests. This was computed by taking the average of the three ISI conditions for each individual. All *p-values* were submitted to Holm-Bonferroni corrections for multiple comparisons[81], using the *p.adjust* of the *stats* package in R[82].

RESULTS

Table 1 shows a summary of the included participants' IQ, performance on the working memory task, and number of psychotic symptoms. Working memory scores were only available for a subset of the individuals in the neurotypical group. Two-sample independent-means *t* tests were used to test for group differences. When the assumption of the homogeneity of variances was violated, *Welch* corrections were applied to adjust degrees of freedom. Statistical analyses confirmed that the groups differed significantly in IQ, working memory, and number of psychotic symptoms presented. There were significantly more females than males in each group, but no differences in sex between groups. Age did not differ between groups.

Table 1. Characterization of neurotypical and 22q11.2DS individuals included in the analyses: age, sex, IQ, working memory, and number of psychotic symptoms presented.

	Neurotypical controls	22q11.2DS	t-test	Cohen's d
Age	M=22.43; SD=7.27	M=22.67; SD=7.20	t=-0.11, df=39.40, p=.92	d=-0.03
Sex	8 males, 13 females	6 males, 15 females	-	-
IQ	M=113.75; SD=15.35	M=72.95; SD=13.19	t=9.02, df=37.16, p<.01	d=2.85
Working memory	M=103.46; SD=13.81	M=78.50; SD=15.77	t=4.94, df=25.80, p<.01	d=1.68
N symptoms	0	M=0.95; SD=1.12	t=-3.91, df=20.00, p<.01	d=-1.21

Figure 1 shows correlations between number of psychotic symptoms presented, IQ and working memory. Lower IQ (r = -.56, p < .01) and poorer working memory (r = -.59, p < .01) scores were observed in those individuals presenting more psychotic symptoms.

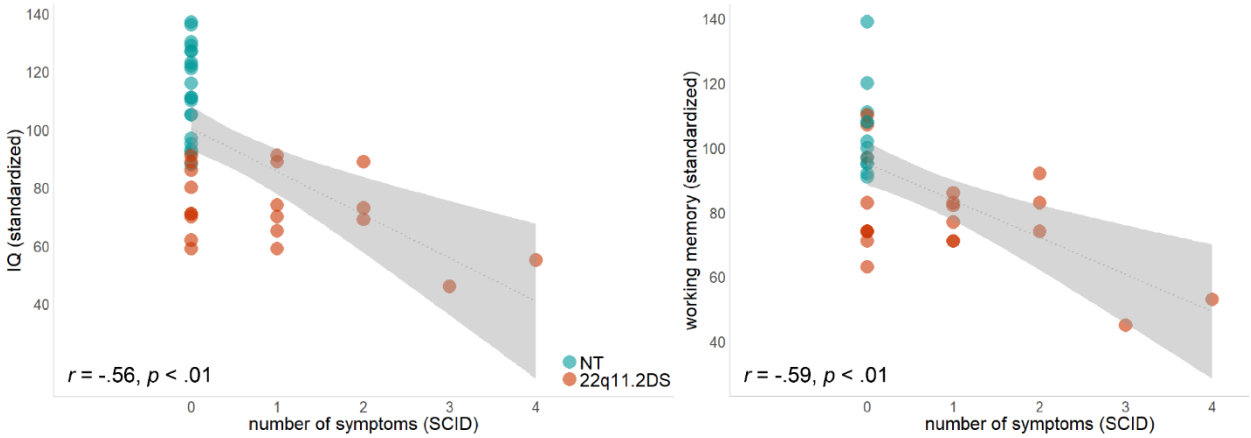

Figure 1. Pearson correlations between IQ scores and number of psychotic symptoms, and working memory performance and number of psychotic symptoms.

Figure 2 shows the averaged ERPs and topographies for the time windows of interest (N1 and MMN), per SOA and by group. Overall, 22q11.2DS data were characterized by increased amplitude auditory evoked responses (Figure 2B) and greater variability (Figure 2C).

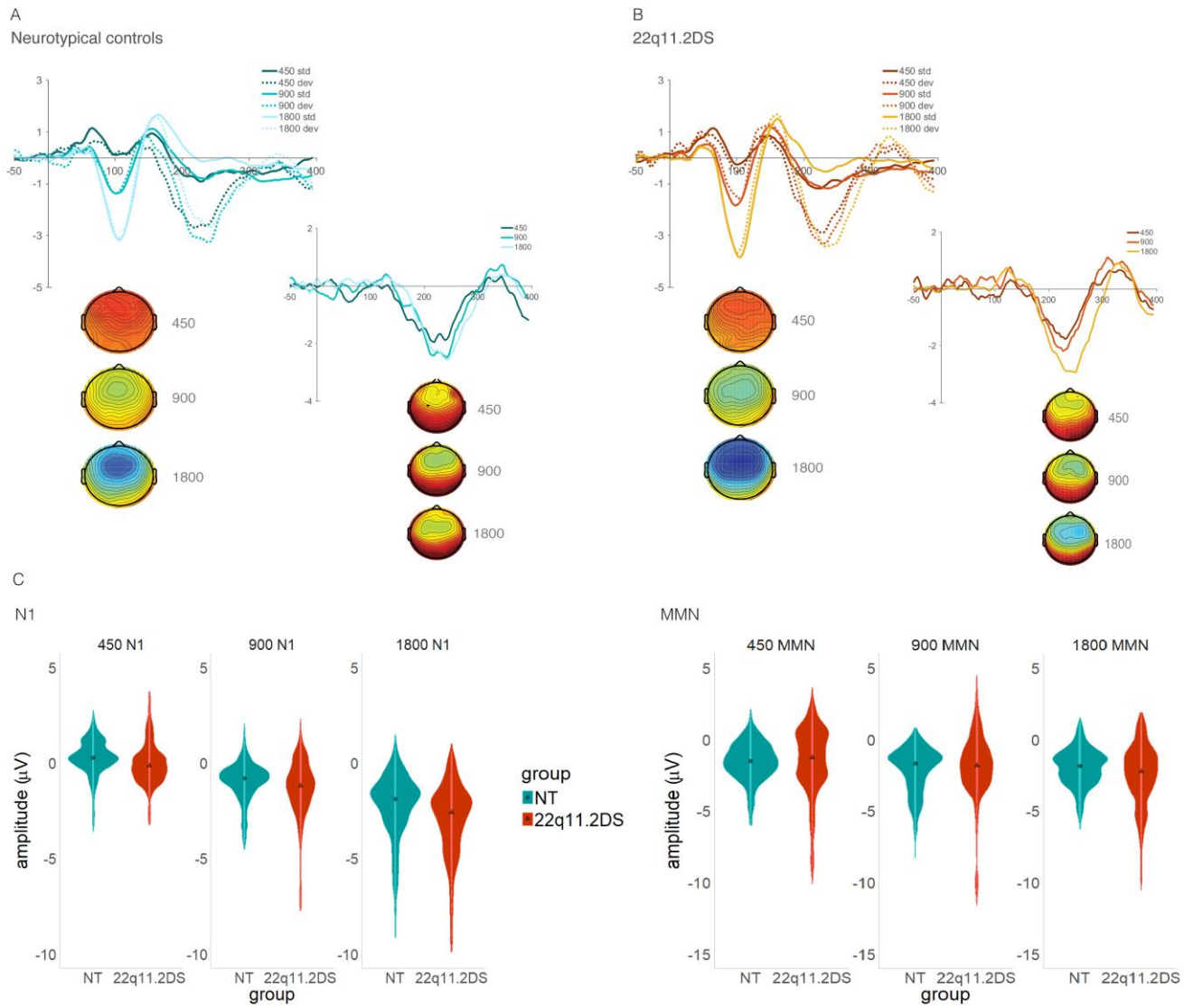

Figure 2. Panel A: Upper left, averaged Standard and Deviant ERPs and Standard topographies per SOA for the NT group at FCz; Lower right, smaller plot, shows MMN, i.e., differences between standards and deviants; topographies are organized from the shorter (450 ms) to the longer (1800 ms) SOA. Panel B: Averaged ERPs and topographies per SOA for the 22q11.2DS group at FCz (smaller plot shows MMN, i.e., differences between standards and deviants); topographies are organized from the shorter (450 ms) to the longer (1800 ms) SOA. Panel C: Violin plots showing distribution of amplitudes for N1 and MMN per group and SOA at FCz. Black square indicates median.

Separate mixed-effects models were implemented to analyze the N1 and MMN data, using the *lmer* function in the *lme4* package[83] in R[82]. Mean amplitude at FCz was the numeric dependent variable. For the N1, only standards were considered. For the MMN, mean amplitude represents the difference between standards and deviants. Group (NT = −0.5, 22q11.2DS = 0.5) was a contrast-coded fixed factor, and SOA a numeric fixed factor. Subjects and SOA were added as random factors. Models were fit using the maximum likelihood criterion. *P* values were estimated using *Satterthwaite* approximations.

For the N1, no significant main effect of group was found. There was an effect of SOA: Both 900 ms ($ß$ = -1.41, SE = 0.07, $p < .001$) and 1800 ms ($ß$ = -2.97, SE =, 0.07 $p < .001$) SOAs elicited larger

responses than the 450 ms SOA. There was also an interaction between group and SOA, with the difference between the 450 ms and the 1800 ms SOA being larger in 22q11.2DS than in the neurotypical control group (*ß* = -0.41, SE = 0.14, $p < .01$). *Post-hoc* analyses conducted to clarify the basis for this interaction revealed differences between the groups for all SOAs: 450 ms SOA ($t = 2.86$, $df = 407.89$, $p < .01$, $d = 0.29$), 900 ms SOA ($t = 2.68$, $df = 362.91$, $p < .01$, $d = 0.26$) and 1800 ms SOA ($t = 3.73$, $df = 414.12$, $p < .01$, $d = 0.36$), with individuals diagnosed with 22q11.2DS presenting with increased amplitudes compared to their neurotypical peers. N1 amplitudes did not correlate significantly with IQ, working memory, or number of psychotic symptoms.

As observed in the N1 time window, there was no significant effect of group for the MMN. Once again, there was an effect of SOA, though in the opposite direction of what was expected: Both the 900 ms SOA (*ß* = -0.46, SE = 0.08, $p < .001$) and the 1800 ms SOA (*ß* = -0.68, SE = 0.08, $p < .001$) conditions elicited larger MMN responses than the 450 ms SOA. The effect of the interaction between group and SOA was also significant here: The difference between the 450 ms and the 1800 ms SOA was larger in the 22q11.2DS group than in the neurotypical control group (*ß* = -0.55, SE = 0.15, $p < .001$). *Post-hoc* analyses conducted to clarify this interaction revealed differences between the groups in the 1800 ms SOA, with individuals diagnosed with 22q11.2DS appearing to present increased amplitudes when compared to their neurotypical peers. However, this result did not hold after correcting for multiple comparisons ($t = 2.13$, $df = 333.90$, $p = .102$). In contrast to what was observed for the N1 component, MMN amplitudes correlated significantly with working memory performance ($r = -.42$, $p = .05$), with individuals who scored lower on the working memory tasks presenting decreased MMN amplitudes (Figure 3). *Post-hoc* correlation tests examining the two groups separately were performed to clarify this relationship. This correlation appears to have been mainly driven by the 22q11.2DS group, as can be appreciated in Figure 3 B and C: While the association between working memory and MMN amplitudes was significant for the 22q11.2DS ($r = -.48$, $p < .05$), that was not the case for the neurotypical controls ($r = -.56$, $p > .05$).

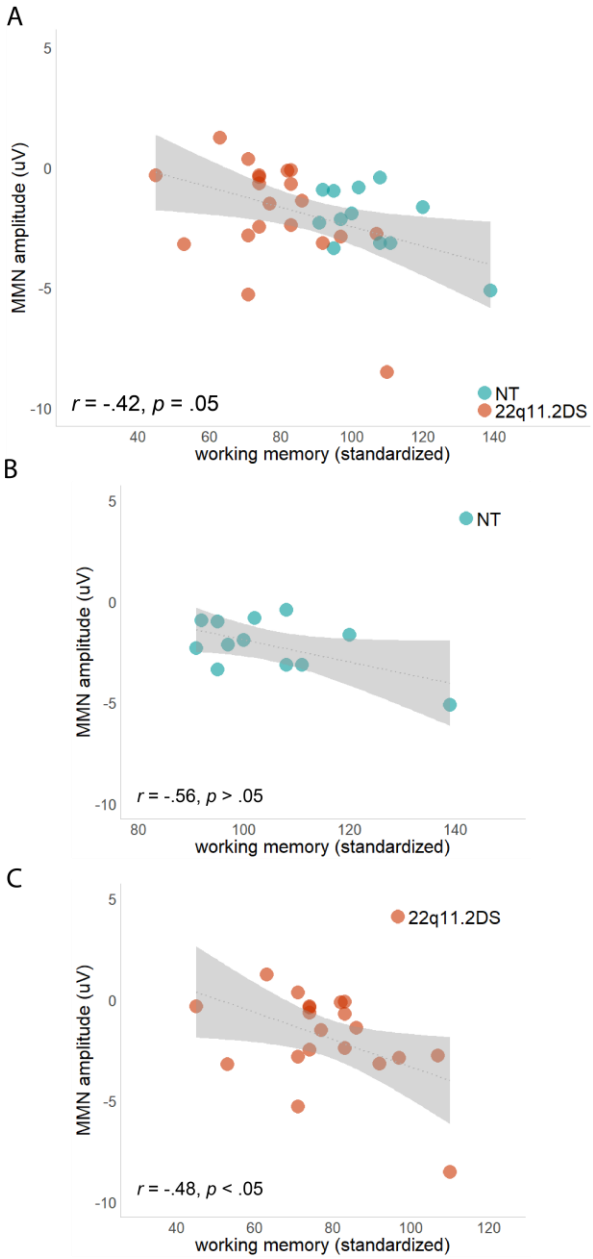

Figure 3. Pearson correlation between MMN amplitude and working memory performance across groups (A) and separately for neurotypical controls (B) and individuals diagnosed with 22q11.2DS (C).

DISCUSSION

Here, we characterized early auditory sensory processing in a group of adolescents and adults with 22q11.2DS, with and without psychotic symptomatology, and related those measures to cognitive and clinical characteristics in order to assess their potential informativeness with regard to vulnerability, conversion, and progression of psychosis.

First, when compared to their neurotypical peers, individuals diagnosed with 22q11.2DS presented increased N1 amplitudes. Larger auditory evoked potentials have also been described in a

22q11.2DS mouse model: Loudness dependent P1-N1-P2 amplitudes were increased in mice with the deletion[84]. Likewise, two human studies looking at auditory processing in 22q11.2DS showed enhanced early sensory responses in 22q11.2DS as reflected in an increased N1[73, 85]. This increase has been associated to elevated activity in the anterior cingulate and dorsomedial frontal cortex[73]. It could additionally be explained by alterations in the cortical glutamate N-methyl-D-aspartate (NMDA) receptors[85]: Increased N1 responses have been reported after administration of ketamine, an NMDA antagonist[86, 87]. This enhanced N1 in 22q11.2DS sits in stark contrast with findings in schizophrenia, where N1 is instead typically reduced compared to controls[45-48, 88, 89]. These findings suggest that enlarged N1 amplitude is a marker of 22q11.2DS, rather than vulnerability for psychosis. Moreover, an enhanced N1 could reflect a lack of adaptation in 22q11.2DS. Typically, repeated presentation of an auditory stimulus leads to reductions in amplitude of the response. Inhibitory processes could thus be impaired in 22q11.2DS, leading to an overall amplified sensory response.

Second, the groups did not differ in MMN amplitude, with the exception of a larger difference between the shortest and the longest SOAs in 22q11.2DS, when compared to the control group. Previous studies on MMN in 22q11.2DS have yielded somewhat inconsistent evidence (for a review, see[90]): Whereas some studies have found reduced pitch, duration and frequency MMNs[85, 91], others failed to show differences between individuals with 22q11.2DS and their neurotypical peers[72, 92]. Such inconsistencies in MMN differences may reflect the phenotypic heterogeneity that is characteristic of 22q11.2DS, as well as, possibly, methodological and stimulus related differences. Adding to the range of findings, here we observed that whereas at characteristic stimulation rates for MMN studies the response appeared typical, at the longest SOA it increased in amplitude relative to the shortest SOA. This contrasts with an expected attenuation of MMN amplitude with increasing SOAs in this group, due to weaker memory traces (see[75]). Previous work from our lab using the same paradigm showed that increasing SOA effectively indexed weakness in maintenance of the memory trace in Rett Syndrome[74]. An increase in MMN amplitude for the 22q11.2DS group at the longest SOA is thus hard to reconcile with the extant literature and, to our knowledge, has not been previously reported.

That individuals with 22q11.2DS did not show reduced MMN responses is also at odds with evidence showing decreased amplitudes in those at-risk of developing schizophrenia[45-48, 56-60, 88]. A plausible hypothesis is that reduced auditory sensory amplitudes are only characteristic of those 22q11.2DS individuals with greatest risk for psychosis and therefore not clearly observable here, given the mixed nature of this 22q11.2DS sample (individuals with and without psychotic symptoms). And, indeed, analyses taking into consideration individual differences revealed an association between MMN amplitudes and working memory: Worse performance on working memory measures was associated with reduced MMNs. Importantly, those individuals with more psychotic symptoms presented poorer working memory and lower IQ, which may suggest an association between worse cognitive and psychiatric

profiles and MMN reductions. This would accord with evidence in 22q11.2DS studies showing associations between MMN amplitudes and working memory[91] and between working memory and psychotic symptomatology severity[93]. Moreover, it would be consistent with the conceptualization of cognitive functioning as a vulnerability marker for psychosis[94]. In particular, working memory deficits are cardinal in schizophrenia[95, 96] and have been argued as a risk factor for psychosis[97, 98].

MMN reductions, observed here for those individuals with 22q11.2DS with lower working memory scores, could be caused by deficient auditory sensory memory-trace formation[99], which has been hypothesized to reflect disturbances of glutamatergic NMDA-receptor-mediated neurotransmission[100]. One of the genes responsible for glutamatergic transmission in the brain is the proline dehydrogenase (PRODH) gene, located on chromosome 22q11. Disruptions in NMDA-mediated glutamatergic transmission have been demonstrated in rats with elevated concentrations of L-proline[101], as well as in Prodh-deficient mice[102]. A mouse model of 22q11.2DS found those mice to display increased locomotor activity in response to NMDA-receptor antagonists, but only after puberty, suggesting the potential of this specific mouse to model the impaired NMDA neurotransmission in idiopathic schizophrenia and in those individuals with 22q11.2DS who go on to develop a psychotic disorder[84]. Second, the reduced MMN may be suggestive of a dampened frontal attention-orienting function[103]. Attentional orienting has been argued to be impaired in 22q11.2DS and to be one of the mechanisms mediating the cognitive decline during the so-called prodromal stage in those individuals with the deletion presenting psychotic symptomatology[92]. Third, loss of grey-matter volume in the left-hemisphere Heschl's gyrus could also be reflected in an MMN reduction and explain speech perception deficits and speech sound-related hallucinations[104]. Reductions in temporal grey matter have also been reported in 22q11.2DS[38].

Lastly, individuals diagnosed with 22q11.2DS had, as expected, lower IQ scores and impaired working memory [18, 105-107]. Though intellectual disability is quite prevalent in 22q11.2DS, its causes are not well understood. Several genes have been identified as potential candidates: For instance, *Tbx1* has been implicated in brain development and may thus have a role in cognitive deficits[108]; PRODH mutations are associated with intellectual disability, and are found in about one-third of the individuals diagnosed with 22q11.2DS[109]. Regarding working memory, the copy number elevations of catechol-O-methyl-transferase (COMT) have been associated with such impairments, not only in 22q11.2DS[110], but also in schizophrenia[111] (but see[112] for different findings). COMT mutations have been argued to result in increased dopamine degradation in the frontal lobes, which could potentially provide a molecular basis for some of the symptomatology associated with both schizophrenia and 22q11.2DS[113, 114]. Additionally, increased variability was observed in the 22q11.2DS group, in line with the remarkable variability in expression described in the syndrome[6,115, 116]. Though here we focus on the distinction between individuals with and without psychotic symptoms, other subgroups with different cognitive and neural

profiles may co-exist within 22q11.2DS. The definition of such subgroups would not only add to the understanding of the phenotype, but also, potentially, impact intervention.

In summary, using a passive oddball paradigm, we show an enhanced N1 in 22q11.2DS. Interestingly, MMN amplitudes correlated with working memory scores: Those who showed relatively decreased amplitudes, presented poorer working memory performance. The simultaneous presence of an increased N1 and a decreased MMN (for a subset of the 22q11.2DS group), may suggest that two different mechanisms are at play, impacting the neural response patterns reported here: One intrinsic to 22q11.2DS which results in increased sensory responses and another associated with psychosis and leading to decreased MMN responses. That reduced MMNs were observed only for those individuals with poorer working memory performance (and, importantly, psychotic symptomatology) and not for the 22q11.2DS group as whole, is in accordance with previous evidence of unimpaired MMN in first-degree relatives of individuals diagnosed with schizophrenia and the consequent hypothesis that the MMN deficit observed in schizophrenia might be a consequence of the disorder and not endophenotypic[69].

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