

Abnormal Auditory Processing and Underlying Structural Changes in 22q11.2 Deletion Syndrome

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The 22q11.2 deletion syndrome (22q11.2 DS), one of the highest genetic risk for the development of schizophrenia, offers a unique opportunity to understand neurobiological and functional changes preceding the onset of the psychotic illness. Reduced auditory mismatch negativity response (MMN) has been proposed as a promising index of abnormal sensory processing and brain pathology in schizophrenia. However, the link between the MMN response and its underlying cerebral mechanisms in 22q11.2 DS remains unexamined. We measured auditory-evoked potentials to frequency deviant stimuli with high-density electroencephalogram and volumetric estimates of cortical and thalamic auditory areas with structural T1-weighted magnetic resonance imaging in a sample of 130 individuals, 70 with 22q11.2 DS and 60 age-matched typically developing (TD) individuals. Compared to TD group, the 22q11.2 deletion carriers reveal reduced MMN response and significant changes in topographical maps and decreased gray matter volumes of cortical and subcortical auditory areas, however, without any correlations between MMN alteration and structural changes. Furthermore, exploratory research on the presence of hallucinations (H⁺/H⁻) reveals no change in MMN response in 22q11.2DS (H⁺ and H⁻) as compared to TD individuals. Nonetheless, we observe bilateral volume reduction of the superior temporal gyrus and left medial geniculate in 22q11.2DSH⁺ as compared to 22q11.2DSH⁻ and TD participants. These results suggest that the mismatch response might be a promising neurophysiological marker of functional changes within the auditory pathways that might underlie elevated risk for the development of psychotic symptoms.

Key words: auditory processing/medial geniculate volume reduction/DiGeorge Syndrome/psychosis/hallucinations

Introduction

The 22q11.2 deletion syndrome (22q11.2DS; also identified as velo-cardio-facial or DiGeorge Syndrome) is a multisystem syndrome caused by an interstitial microdeletion of 1.5–3 megabases located on the chromosome 22 that implicates the deletion of 35–60 known genes, many being critical for normal brain development.¹ This syndrome affects 1 in 4000 live births^{2,3} and is one of the highest genetic risk factors for the development of psychosis⁴ with a percentage of 30%–40% of the afflicted adults being diagnosed with schizophrenia spectrum disorders.⁴

The 22q11.2 DS is associated with widespread thinner cortical gray matter and altered white matter microstructural organization in major cortico-cortical and thalamo-cortical tracts^{5,6} that might predispose 22q11.2 deletion carriers to elevated risk of developmental neuropsychiatric disorders, such as attention deficit disorder, anxiety disorder, and psychosis.⁴

Neuroanatomic alterations associated with schizophrenia expression in 22q11.2 DS involve significantly thinner cortex in the left superior temporal gyrus (STG), lateral occipital cortex, and superior medial frontal lobe.^{5,7,8} In addition, progressive volumetric decreases in temporal areas predicted psychotic symptom development in 22q11.2 DS youth.^{8,9} Moreover, high genetic liability to schizophrenia was associated with progressive cortical thinning, especially within the superior temporal cortex.¹⁰

Consequently, the 22q11.2 DS offers a unique opportunity to identify brain changes related to schizophrenia and to detect behavioral symptoms at their early stage. Although many studies on 22q11.2 DS emphasize

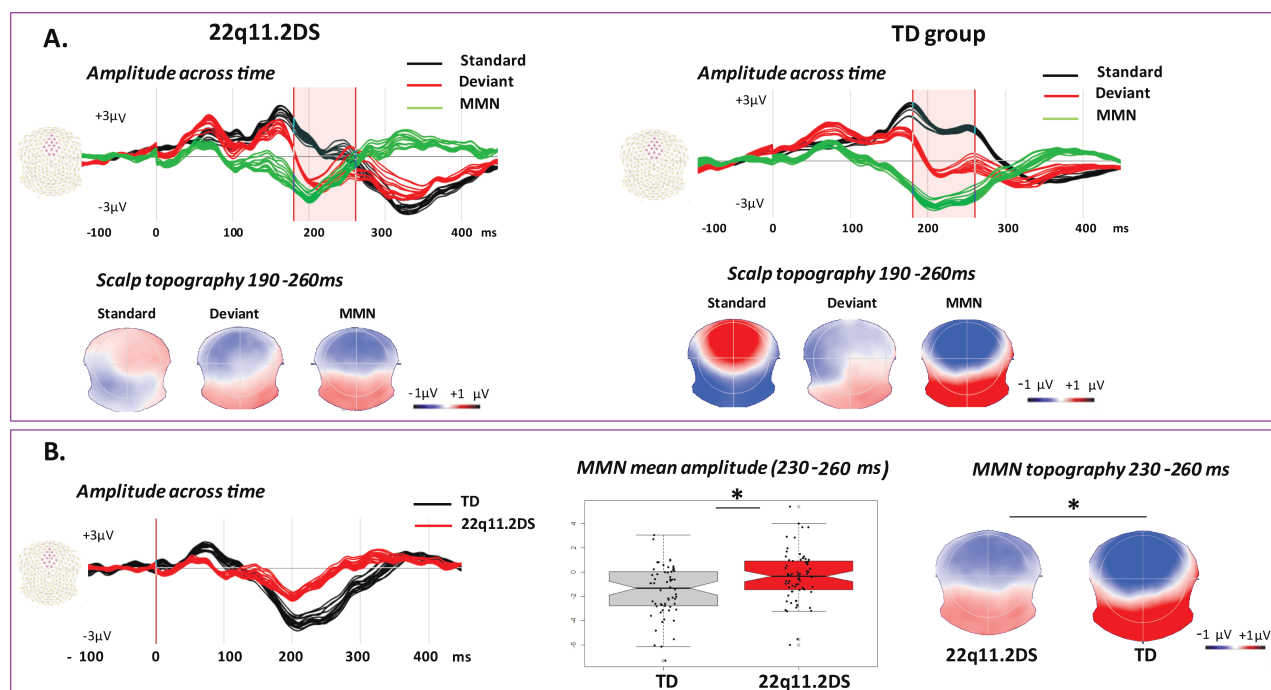


Fig. 1. (A) The amplitude across time of auditory ERPs and the difference waveform (red, the deviant sound; black, the standard sound; green, the difference waveform) over a cluster of 15 fronto-central channels (displayed in pink alongside) plotted across -100 to 400 ms poststimulation (left side, the 22q11.2 deletion syndrome [22q11.2 DS]; right side, typically developing [TD]). The scalp topographies are displayed for standard ERP, deviant ERP, and the difference waveform over 190 – 260 ms poststimulation. (B) The difference waveform. The mean amplitude across time (red, the 22q11.2 DS; black, the TD); the violin boxplot distribution of the mismatch negativity response (MMN) mean amplitude from 15 fronto-central electrodes calculated over 230 – 260 ms; the MMN scalp potential maps (230 – 260 ms poststimulus).

higher-order cognitive impairments,¹¹ deficits manifest also at lower levels of sensory information processing.^{12,13}

A basic sensory dysfunction measured in patients with schizophrenia and in subjects at high risk of developing this disorder,¹⁴ like 22q11.2 deletion carriers,^{15,16} is reduced auditory mismatch negativity (MMN) response. The auditory MMN is an automatic prediction error signal^{17,18} measured as a negative potential generally between 150 and 250 ms poststimulation¹⁹ with fronto-central negative and posterior positive voltage distribution on the scalp.

The MMN response to frequency deviant sounds rely mainly on the activation of subcortical regions, such as medial geniculate nuclei (MGN), and increase in neural signal strength as it progresses toward primary and secondary auditory cortices.^{20–22} Temporal gray matter volume reduction^{23,24} along with alterations in glutamatergic neurotransmission within the auditory areas²⁵ have been proposed to underlie the reduced MMN observed in patients with schizophrenia. Furthermore, reduced MMN response has been linked to auditory hallucinations, a cardinal feature of schizophrenia,²⁶ and was proposed as an index of brain pathology related to this disorder.^{27,28}

In 22q11.2 deletion carriers, decreased MMN observed during adolescence,¹⁶ a period of considerable brain changes, might also indicate cortical gray matter loss over

temporal cortical areas^{7,29} and aberrant thalamo-cortical projections, from MGN to the auditory cortices.^{30,31} To test this hypothesis, the current study investigates the link between the structural volumetric changes within the cortical and thalamic auditory areas and the MMN in participants with 22q11.2 DS compared to typically developing (TD) individuals. Based on prior investigations indicating that scalp electroencephalogram (EEG) can sense both cortical and thalamic activation,³² we focus on three main regions of interest previously reported to be reduced in 22q11.2 deletion carriers that might have an impact on the MMN^{5,31,33}: the thalamus (MGN), the primary auditory area (transverse temporal gyrus), and the secondary auditory area (STG).

Given the high presence of subthreshold positive symptoms (32%) in 22q11.2 deletion carriers,³⁴ the present study additionally explores if the MMN deficit is more pronounced in 22q11.2 deletion carriers with hallucinations compared to 22q11.2 DS deletion carriers without hallucinations and TD participants.

To our knowledge, this is the first study to investigate the link between the MMN measured at the scalp level with high-density EEG and the volumetric estimates of underlying cortical and thalamic auditory areas derived from magnetic resonance imaging (MRI) T1 structural data within this clinical population.

Methods

Participants

A sample of 130 participants was included, 70 with confirmed de novo 22q11.2 microdeletion and 60 TD participants, aged between 6 and 25 years (for demographics, see Table 1). The presence of the microdeletion was confirmed using quantitative fluorescence polymerase reaction.

For exploration research on hallucinatory experiences, we divided our data sample into 3 groups: 22q11.2 deletion carriers (H^+) experiencing moderate-to-severe auditory/mixed (auditory + visual) hallucinations, 22q11.2DS(H^-) without hallucinations at the time of data recording, and TD individuals (demographics, Table 2). The patients simply endorse both auditory and visual hallucinations. We excluded 22q11.2 deletion carriers with missing data regarding their hallucination status and participants under 10 years old (both 22q11.2 DS and TD).

The participants with 22q11.2DS were recruited through advertisements in patient association newsletters, while the TD individuals were recruited through the local school system and among the siblings of the participants with 22q11.2 DS. Written informed consent was obtained from participants and their parents. The study was approved by the ethical committee of the University of Geneva, Switzerland.

The participants' neuropsychiatric and cognitive profiles were evaluated by a trained psychiatrist (S.E.). Parents of individuals with 22q11.2 DS under 18 years were interviewed using the computerized Diagnostic Interview for Children and Adolescents³⁵ to identify the presence of psychiatric disorders in their children, while participants with 22q11.2 DS over 18 years old were interviewed using the Structured Clinical Interview for DSM-IV Axis I disorders.³⁶ The participants were tested on a full Wechsler Intelligence Scale for children (WISC-III-R/WISC-IV) or the Wechsler Adult Intelligence Scale (WAIS-III/WAIS-IV) for participants older than 17 years old.^{37–39}

We assessed the presence of moderate-to-severe (scored from 3 to 6) abnormal perceptions/hallucinations by means of the Structured Interview for Psychosis-Risk Syndromes (SIPS-scale P4). SIPS use a 7-point severity scale from 0 to 6 and is based on the participants' answer, so children <10 years old are usually not evaluated.

Stimuli

Sequences of auditory stimuli were presented binaurally using intra-aural insert earphones (Etymotic Research) at an intensity of 65 dB SPL in 1 block of 600 tones. Standard stimuli were pure tones of 1000 Hz frequently released ($n = 480$), while deviant stimuli were pure tones of 1200 Hz more rarely

Table 1. Demographical and clinical data

	TD ($n = 60$)	22q11.2 DS ($n = 70$)
Age (mean age $\pm$ SD; range)	14.02 $\pm$ 4.37; 6–23	15.29 $\pm$ 5.06; 7–25
Gender (M/F)	32/28	34/36
Full-scale IQ (mean $\pm$ SD)	110.63 $\pm$ 14.06	72.55 $\pm$ 11.71
Psychiatric diagnosis (n)		ADHD (20) Phobia (9) Major depression (5) Generalized anxiety (5) Schizoaffective disorder (2)
Medication		
Antipsychotic (n)		2
Antidepressant (SSRIs; n)		7
Methylphenidate (n)		9

Note: TD, typically developing; 22q11.2 DS, 22q11.2 deletion syndrome; ADHD, attention deficit hyperactivity disorder.

released ($n = 120$). The stimuli were randomly presented with a standard to deviant ratio of 8:2 via E-prime 1 (Psychology Software Tools Inc). The stimuli were 100 ms long and were presented with an interstimulus interval (ISI) of 520 ± 2 ms. Ten participants received the auditory stimuli with a mixed ISI of 507 ± 2 ms and 520 ± 2 ms due to a brief issue with the presentation computer. This ISI variation was independent of group membership and affected both standard and deviant stimuli.

Throughout the stimuli presentation, the participants were comfortably seated inside a Faraday shielded room watching a silent cartoon movie used as a visual distracter. Additionally, we performed a brief behavioral test after the MMN paradigm administration where the participants were asked to actively count the deviants, and no behavioral differences are observed between the participants with 22q11.2 and TD individuals ($n = 94$; $t(df92) = 1.13$, $P = .25$).

Data Acquisition

EEG data were continuously recorded with a sampling rate of 1000 Hz using a 256-electrode Hydrocel cap (EGI-Philips Healthcare) referenced to the vertex (Cz). The T1-weighted scans were acquired with 2 different scanners: a 3T Siemens Trio was used for the first 51 scans and a 3T Siemens Prisma used for the remaining 79 scans at the Center for Biomedical Imaging in Geneva. The proportion of scans with each scanner type did not differ between patients with 22q11.2 DS and TD ($\chi^2 = 0.3$, $P = .57$). The parameters for the acquisition

Table 2. Demographical and clinical data (subsamped participants)

	TD (<i>n</i> = 48)	22q11.2 DS(H [−]) (<i>n</i> = 39)	22q11.2 DS(H ⁺) (<i>n</i> = 16)
Age (mean age ± SD)	15.32 ± 3.74	17.19 ± 4.26	16.12 ± 3.65
Gender (M/F)	27/21	20/19	7/9
Full scale IQ (mean ± SD)	110.21 ± 13.31	73.51 ± 13.14	68.06 ± 9.46
Psychiatric diagnosis (<i>n</i>)			
ADHD		9	6
Phobia		3	2
Major depression		2	1
Generalized anxiety		3	1
Schizoaffective disorder		0	2
Psychotic symptoms		NA	Moderate (14)
Severity (<i>n</i>)			Severe (2)
Medication			
Antipsychotic (<i>n</i>)		0	2
Antidepressant (<i>n</i>)		4	4
Methylphenidate (<i>n</i>)		7	2

Symptoms score (SIPS-scale P4): moderate 3–4, severe 5–6. Abbreviations are explained in the first footnote to table 1.

of structural images with a T1 sequence were repetition time = 2500 ms, echo time = 3 ms, flip angle = 8°, acquisition matrix = 256 × 256, field of view = 23.5 cm, slice thickness = 1.1 mm, and 192 slices.

Data Processing

EEG Data. The data were band-pass filtered between 1 and 40 Hz using noncausal Butterworth filters. Independent component analysis was applied to remove eye movement and electrocardiogram artefacts⁴⁰ using a Matlab script based on the EEGLab runica function⁴¹ (scn.ucsd.edu/eeqlab/). Epochs with movement artifacts exceeding 60 μV were excluded. Peristimulus epochs (−100/+450 ms) were averaged for each participant separately for standard and deviant stimuli after applying a baseline correction by subtraction of the averaged prestimulus 100 ms. The accepted epochs did not differ between the 2 groups (TD 75.31 ± 11.09; 22q11.2 DS 75.44 ± 10.10, mean ± SD; *t*(128) = −0.06, *P* = .94). Averaged data were recalculated to the common average reference. Mismatch responses were then individually calculated by subtracting the standard evoked potential from the deviant-evoked potential. We identified the window of MMN component in the group average difference waveform and we quantified the MMN amplitude by averaging 15 fronto-central channels around FCz for each individual

over 230–260 ms poststimulus. This mean amplitude was used for further analyses. The preprocessing steps were performed using the free academic software Cartool and detailed in the [supplementary material](#).

MRI Data. T1-weighted images underwent fully automated image processing with FreeSurfer version 6.0, comprising skull stripping, intensity normalization, reconstruction of the internal and external cortical surface, and parcellation of subcortical brain regions.⁴² The cortex was automatically subdivided into 34 bilateral cortical region of interests (ROIs) by using the Desikan–Killiany⁴³ atlas. Thalamic nuclei were segmented with a new technique implemented in FreeSurfer version 6.0⁴⁴. A probabilistic atlas of the thalamus based on Bayesian inference was built combining histological delineation of 26 nuclei with in vivo manual segmentation of the thalamus and surrounding regions.⁴⁴ The quality of the segmentation was ensured by visual inspection, following a quality control procedure used in previous work.^{31,45} Due to the specific hypotheses of the study, only the bilateral volumes of the STG, transverse gyrus, and MGN were considered for the analyses.

Statistical Analyses

Group differences in MMN mean amplitude were examined using a 1-way ANCOVA with age as a covariate. Topographic differences of MMN scalp potential maps were assessed using a nonparametric topographical bootstrapping approach with preset alpha level for the significance of *P* < .05, and a temporal criterion of 20 ms of continuous significance.⁴⁶

Group differences in gray matter volumes were examined using linear models, adjusted for gender, age, intracranial volume, and scanner. Cohen’s *d* effect size estimates⁴⁷ were derived from *t*-values and degrees of freedom (*df*). Since the inclusion of IQ as a covariate in the analyses could be misleading and conduct to a bias, we did not include the IQ as a covariate in our statistical analysis.^{48,49}

To understand whether MMN mean amplitude can be predicted based on age, group, and gray matter volumes, we used multiple linear regression analysis. Regarding the exploratory analyses between 22q11.2DS(H[−]), 22q11.2DS(H⁺), and the TD groups, we applied 1-way ANCOVA to measure the differences in MMN mean amplitude (controlling for age) and 1-way MANCOVA to compare gray matter volumes (controlling for age, gender, intracranial volume, and scanner). For pairwise comparisons, we used the Sidak correction.

To measure the association between the MMN mean amplitude, gray matter volumes, and IQ, 2-tailed partial Pearson correlation coefficient was applied with an alpha level for significance of *P* < 0.01, with bootstrapping methods for multiple comparison and controlling for age. To measure the association between the MMN

Table 3. The effect sizes and *P*-values for all the ROIs

Region	<i>F</i> value	Adjusted <i>R</i> ²	<i>t</i> -value	<i>P</i> -value	Cohens' <i>d</i>	Group × Age (<i>t</i> / <i>P</i> -values)
lhMGN	16.39	0.37	-4.89	3.66e-06	-0.87	-0.23/.81
rhMGN	14.83	0.34	-4.01	.0001	-0.72	-0.007/.99
lhTG	6.20	0.16	-2.92	.0044	-0.52	-0.25/.80
rhTG	3.35	0.08	-2.66	.0086	-0.47	0.33/.73
lhSTG	14.22	0.33	-3.22	.0016	-0.57	0.09/.93
rhSTG	18.33	0.40	-3.92	.0001	-0.70	0.59/.55

Note: [The linear model used for the group comparison: Volume ~ Group + Age + Gender + ICV + Scanner (+Group × Age). *F* (5,124) and *P* < 0.05 for all comparisons.]

mean amplitude and symptoms severity scales assessed with SIPS, Spearman's rank correlation coefficient was applied with an alpha level for significance of *P* < 0.01, with bootstrapping methods for multiple comparison. If the assumptions of normality or homogeneity were violated, additional nonparametric tests were used (Mann–Whitney *U* test/Kruskal–Wallis *H* Test, with Bonferroni adjustments).

Results

We observe a significant difference in IQ (*t* = 16.6, *df* = 125, *P* < .0001), but no difference in gender distribution (χ^2 = 0.3, *P* = .58) or age (*t* = -1.4, *df* = 128, *P* = .13) between the 2 groups.

MMN Response

The mean amplitude is significantly smaller in 22q11.2 deletion carriers as compared to TD individuals, ANCOVA results: *F*(1, 127) = 9.24, *P* = .003 whilst adjusting for age. This significant reduction in amplitude co-occurs with a significant change in scalp potential maps for the 22q11.2 DS group (between 230 and 260 ms poststimulus; topographical bootstrapping; *P* < .05).

No significant correlations are observed between MMN and IQ scores in the 2 groups. However, a negative correlation is measured between the MMN mean amplitude and P2 (persecutory ideas; *r* = -.44, *P* = .001; CI [0.18, 0.66]) severity scales in 22q11.2 DS.

No group × age interaction is observed (*F*(3, 126) = 5.93, *t* = 0.8, *P* = .37). No statistical differences in MMN amplitude between 22q11.2 DS individuals with ADHD, 22q11.2 DS individuals with other diagnosis (major depression, generalized anxiety, and phobias), and 22q11.2 DS individuals without a diagnosis (*F*(2, 67) = 2.1, *P* = .11) is observed.

Volumetric Differences

Overall, when compared to TD individuals, the deletion carriers express smaller relative gray matter volumes in all tested auditory-related areas, MGN, transverse temporal

gyri, and STG. No group × age interaction is observed. All the effect sizes and *P*-values for all the ROIs are presented in Table 3.

MMN and Gray Matter Volumes

No significant correlations between the mean amplitude of MMN and gray matter volumes are measured in 22q11.2 DS or TD groups whilst correcting for age. Additionally, the results of multiple regression analysis indicate the model as a significant predictor for the MMN amplitude (*F*(8,121) = 2.99, *P* = .004, *R*² = 0.17), considering the factors age (*t* = 1.7, *P* = .07) and group (*t* = 2.08, *P* = .03) as the most important predictors in the model (multicollinearity of the variables: tolerance >0.3, variance inflation factor [VIF] <4).

Hallucinations and the MMN Response

There are no differences in gender distribution (χ^2 = 0.93, *P* = .62), scan type (χ^2 = 1.5, *P* = .47), or age (*F*(2, 100) = 2.3, *P* = .09) between the three groups. The results of 1-way ANCOVA show no significant differences in mean amplitude between the 3 groups (*F*(2, 99) = 1.8, *P* = .17). However, the results of 1-way MANCOVA reveal significant differences in gray matter volumes between the groups (*F* (12,182) = 3.5, *P* < .0001, Wilks' Λ = 0.66, partial η^2 = 0.19) with the following results: (1) when comparing the 22q11.2 DS(H⁺) with 22q11.2 DS(H⁻) participants, lhSTG is decreased in volume (*P* = .03); (2) when comparing the 22q11.2 DS(H⁺) with TD participants, the volumes of lhMGN (*P* < .0001), lhSTG (*P* = .002), and rhSTG (*P* = .01) are significantly smaller; (3) when comparing the 22q11.2 DS(H⁻) with TD participants, the volumes of lhMGN (*P* = .001) and rhMGN (*P* < .0001) are reduced significantly (Pairwise comparisons, Sidak correction).

Furthermore, TD, 22q11.2 DS(H⁻) and 22q11.2 DS(H⁺) groups show no significant correlations between MMN amplitude and the volumes whilst correcting for age. The rhMGN, rhTG, and rhSTG volumes are slightly deviating from the normal distribution. The results are reported in [supplementary material](#).

Discussion

The 22q11.2 deletion carriers show reduced MMN response to frequency deviant sounds and significant changes in scalp potential maps, pointing toward functional changes in underlying brain areas accountable for the response, and decreased gray matter volume of cortical and subcortical auditory areas as compared to TD individuals.

The findings are similar to longitudinal studies reporting reduced MMN response¹⁶ and progressive volumetric decreases in temporal areas in 22q11.2 DS youth^{8,29} and cross-sectional studies with large cohorts reporting global thinning of the cortex.^{5,7}

In contrast, other studies reported no significant MMN amplitude reduction to the frequency deviant in 22q11.2 DS.^{15,50} These inconsistencies might be caused by methodological differences, as well as the heterogeneity of phenotypes in 22q11.2 deletion carriers. Nevertheless, Baker et al.¹⁵ found a reduction in the MMN response to duration deviants, while Larsen et al.⁵⁰ noticed an altered functional connectivity from frontal areas to STG in response to frequency deviants. These findings complement ours by adding the connectivity information and focus on duration deviants and indicate that distinct MMN cortical generators underlie different auditory deviants, as reported previously,⁵¹ that may be heterogeneously compromised across 22q11.2DS, in line with findings in schizophrenia.²⁷

Contrary to our hypothesis, we do not observe significant correlations between reduced amplitude of MMN response and decreased gray matter volumes of cortical and subcortical auditory areas. These results, along with topographic differences might indicate an abnormal cortical and/or subcortical activation pattern and yet fail to map a clear relationship between structural and functional changes in the auditory network. Therefore, we presume that, in 22q11.2 DS, reduced MMN might be explained by underlying abnormal functional activity rather than being merely due to dispersed gray matter diminution.

The presence of hallucinations reveals no effect on the MMN amplitude. However, the 22q11.2DSH⁺ group express reduced volume of lhMGN and bilateral STG compared to 22q11.2DSH⁻ and TD participants.

These findings go in line with prior investigations indicating abnormal developmental trajectories of MGN volume and immature pattern of connectivity with primary and secondary auditory cortices in 22q11.2 DS.³¹ Interestingly, MGN was shown to be hyperconnected to auditory cortical regions at rest, with a negative correlation between the connectivity and its volume (the higher the connectivity, the lower MGN volume) in 22q11.2 deletion carriers experiencing auditory hallucinations, suggesting that psychotic deletion carriers exhibit hyperactivity of the brain regions underlying auditory processing at rest and abnormally activate the same network during an auditory task.³¹ In addition, the structural changes, such as left-sided

volume reduction of the STG in 22q11.2DSH⁺ group might be related to hallucinatory experiences as previously reported in both 22q11.2 DS youth^{8,9} and schizophrenia.¹⁰

Consequently, our findings indicate that structural changes, such as reduced volumes of lhMGN and lhSTG, might predispose individuals with 22q11.2 DS to elevated risks for the development of psychotic symptoms. Importantly, we must highlight some limitations. The 22q11.2 deletion carriers express heterogeneous levels of neuropsychiatric disorders and medication status that might influence our results. The subsampled data was very small and unevenly distributed; thus, the analysis should be considered as exploratory and the results interpreted with caution. Additionally, we used the regions of interest undivided into functional subregions and we did not add the duration deviant, which might be relevant for future studies to produce divergent markers for functional deficits in 22q11.2 DS.

In conclusion, we observe schizophrenia-like functional auditory neurophysiological abnormalities unrelated to the structural alterations measured along the auditory pathway. These findings highlight the reduced MMN response as a promising index of abnormal sensory processing and can add value to clinical assessments when aiming to detect abnormal function within the auditory cortical areas involved in the MMN generation.

Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin* online.

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