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Brett Henshey April 1, 2023

Comparison of Cognitive and Psychophysiological Responses between 22q11 Deletion Syndrome Patients and Healthy Controls

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An abstract of
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Abstract

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By Brett Henshey

Introduction: 22q11.2 deletion syndrome (22q11DS) is the most common interstitial-deletion disorder known in humans, occurring in approximately 1 in 4000 live births. 22q11DS is caused by the deletion of up to 3 megabases (Mb) of DNA on the proximal q arm of chromosome 22. 22q11DS patients exhibit a multitude of clinical phenotypes that include abnormal facial features, congenital heart defects, poor muscle development, and various cognitive disabilities. Up to 20-30% of patients with 22q11DS will develop schizophrenia (SCZ) by adulthood, making 22q11DS one of the strongest known genetic predictors of SCZ onset. In this study we examined cognitive, motor-reaction, and speed-of-target-detection performance in 22q11DS individuals to understand the relationship between cognition and psychophysiological responses used in target detection.

Methods: 21 patients with 22q11DS and 31 healthy comparison subjects performed psychophysiology measures, sensorimotor measures, neurocognitive measures, and had prodromal symptoms of SCZ assessed. The neurocognitive measures examined were preservative error rates and responses in the Wisconsin Card Sorting Task (WCST), a test of executive function. Motor function was assessed through a finger tapping task (FTT) (the subjects tapped a key as many times as they could in six ten second rounds for each hand). Reaction time latency to a visual cue was assessed with a reaction time test (RTT) and from a visual oddball task in a mismatch negativity paradigm (MMN). Each subject's prodromal-symptom severity was assessed with the Structured Interview for Psychosis-Risk Syndromes (SIPS). One-way ANOVA tests were conducted for group comparisons with age, sex, socioeconomic status (SES), and education level entered as covariates.

Results: There were four significant group differences: the rates of SIPS positive symptoms ($F(1,30)=5.370$, $p=.029$; SIPS negative symptoms ($F(1,30)=20.916$, $p=<.001$; MMN Frequency Deviant ($F(1,30)=5.241$, $p=.030$; MMN Frequency and Duration Deviant ($F(1,30)=7.813$, $p=.009$. There were no significant differences in either FTT test, RTT, WCST perseverative errors or responses, and the MMN Duration deviant.

Conclusion: The higher rates of SIPS positive and negative symptoms in the 22q11DS group are not surprising considering the likelihood of prodromal symptoms in the 22q11.2 DS population. The differences in the MMN confirm the 22q11.2 DS defects in generating enhanced responses to oddball stimuli, especially when frequency or both frequency and duration deviate from the norm. The lack of significant difference between the two groups in the FTT could suggest basic

motor functions are intact in individuals with 22q11DS. The similarity in reaction times could indicate that the basic neural processing necessary for target detection processes were intact and functional.

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IRB Approval

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IRB number 111990

BACKGROUND

22q11.2 Deletion Syndrome (22q11DS) is a common disorder caused by a hemizygous deletion of up to 3 megabases (Mb) of DNA on the q11.2 location of Chromosome 22; it occurs in approximately 1 of 4000 live births (Basset & Chow, 1999). This region on the chromosome is prone to rearrangements and deletions because of four low copy repeats (LCRs) located here.~~,~~ Misalignment of LCRs during meiotic recombination contributes to the development of several microdeletion disorders in various locations in the genome (Shaikh, 2000). The 22q11.2 deletion affects anywhere from 30-50 genes depending on the size of the deletion, which is determined by the particular combination of LCRs causing the deletion. Individuals with this disorder suffer from numerous clinical phenotypes such as heart defects, immune problems, abnormal facial structures, and cognitive deficits.

Interestingly, 25-40% of individuals that suffer from 22q11DS will develop schizophrenia (SCZ) early in life, and 50-60% of patients with 22q11DS suffer from prodromal symptoms of SCZ (Shapiro 2011; Schneider 2014). The elevated risk of SCZ associated with 22q11.2DS is consistent with the results of recent moleculear-~~-~~genetic studies that show that susceptibility to SCZ maps to chromosome 22 (Murphy, 2002). Patients with SCZ also have an estimated 80-fold increased chance of carrying this microdeletion as members of the healthy population (Baker and Skuse, 2005). Patients with both 22q11.2 DS and SCZ do not differ from idiopathic SCZ cases in the age of onset and prodromal symptoms, phenotypical expression, or response to different forms of treatments (Baker and Skuse, 2005). These statistics make 22q11.2DS one of the strongest known genetic predictors of SCZ~~1~~ (Schneider, 2014).

SCZ is a neurological disease that is estimated to affect 1-2% of the entire world population. It results in problems with thought, emotional expression, and the ability to interact with the real

world that often last a lifetime (Weinberger & Harrison 2008). The exact cause of SCZ is unknown; however, it has been shown to be extremely heritable, up to 80% (Sullivan et al. 2012). Recent genetic studies have produced a wide variety of results, slowing down the process of understanding the full role genetics play in the development of SCZ. Research has shown that abnormalities in dopaminergic transmission contribute to the development of SCZ, and disturbances in synaptic function can also lead to the onset of symptoms (Weinstein, 2017). Brain scans show that subjects with SCZ possess less gray matter in the frontal and temporal lobes than healthy controls, and some scans have even shown size abnormalities in the hippocampus (Thompson, 2001). However, researchers have yet to strongly confirm a singular definitive pathway to the development of SCZ.

Environmental factors also contribute to onset of SCZ: childhood adversity, poverty, poor nutrition while the mother is pregnant, infections such as chlamydia, and marijuana use during childhood and adolescence have all been linked with SCZ onset (Van Os, 2011). Many prodromal symptoms such as impaired motor function, false beliefs, and loss of touch with reality also associate with elevated risk for development; however, most patients with prodromal symptoms do not enter full psychosis (Addington 2007; Insel 2010). The onset of full SCZ typically will occur during late teens to the early 20s for most individuals, including those that have the 22q11.2 DS. Fully understanding the predictors for SCZ can lead to earlier intervention which drastically improves the outcome for each case.

Unfortunately, there aren't any laboratory or physiological tests that definitively diagnose SCZ or related disorders, so current diagnosis is based on observable behaviors and assessments such as the Structured Interview for Psychosis-risk syndromes (SIPS). According to the DSM-5, patients must exhibit symptoms for at least six months in order to be diagnosed with SCZ,

making it even more difficult to firmly diagnose at- risk individuals. However, the development of diagnostic protocols and treatment procedures are crucial to the protection of at-risk individuals; patients with SCZ have a life expectancy that is 20 years lower than the healthy population because of suicide (Laursen, 2013) and other factors, such as higher rates of tobacco use (Kelly, 2000).

Recent evidence suggests that SCZ in 22q11.2DS manifests similarly to SCZ in those without the deletion disorder, so understanding the effects of 22q11.2DS and how these develop into the onset of SCZ can lead to new insights in the pathophysiology of SCZ. This improvement in understanding could in turn lead to the identification of treatment targets for the disease, which are mostly unknown currently. This study will aim to compare cognitive and psychophysiological responses between 22q11.2DS and healthy controls in the hopes of obtaining a better understanding of the pathophysiology of SCZ.

METHODS

Subjects

There will be up to 50 22q11.2DS and 50 healthy control (HC) subjects between the ages of 16-60; half of each group will be male and half female. 22q11.2DS patients will be recruited principally from a registry of individuals diagnosed and/or followed at Emory University Healthcare or Children's Healthcare of Atlanta or contacted through our engagement with the 22q11.2DS community. All 22q11.2DS subjects must have had the disability molecularly confirmed to qualify. HC will be recruited from the VA system and Emory campus. At the beginning of each test day, subjects will provide written informed consent as approved by the Emory University Institutional Review Board.

Inclusion Criteria:

1. Each subject, or a legal guardian, must give written consent to participate in the study. ,
2. All subjects must pass a urine drug test.
3. All subjects should have the ability to speak English.
4. All subjects should be between the ages of 16-60.
5. Ability to pass a vision and hearing test on test day.
6. Negative for traumatic brain injury (TBI) screening.

Exclusion Criteria:

1. Presence of an ongoing and unstable medical condition.
2. Any hearing impairments that will interfere with the testing.
3. Any current illegal drug usage seen from the toxicology screening (Contact PI if positive for THC).

4. Any hospitalization with the past two months.
5. History of severe head trauma that is deemed significant to interfere with testing
6. IQ < 50
7. HIV or AIDS positive

Clinical predictors for developing SCZ in the 22q11.2DS population are not fully understood. This study will use phenotypic markers commonly seen in SCZ in individuals without 22q11.2DS.

Assessments:

Acoustic Startle Response and Electromyography

The acoustic startle response (ASR) will be measured during this study. The ASR is an innate reflex present in all mammals that allows for quick reactions to potentially harmful stimuli. In humans, the ASR is seen immediately following the occurrence of an unexpected sound stimulus greater than 80dB; the response in humans is observed as a quick eyeblink that can be measured with electromyography (EMG) of the orbicularis oculi muscle. Two electrodes will be placed on the face over the right orbicularis oculi muscle, and one ground electrode will be placed on the subject's right mastoid. Startle latency, the time difference between the stimulus and the ASR as a result of the stimulus traveling through a subcortical circuit, is typically slower in individuals with SCZ and has been shown to be quite heritable (Hasenkamp et al. 2010). ASR latency provides a putative index of neural processing speed. Interestingly, slower latency has also been previously linked to a greater risk of conversion from prodromal symptoms to full SCZ (Cadenhead, 2020). Evidence of slow neural processing, developmental differences and sensitivity to cannabis effects in a sample at clinical high risk for psychosis from the NAPLS Consortium assessed with the human startle paradigm. The effect on latency is even detectable in

patients currently on antipsychotic medications, which makes ASR latency an exceptional phenotypic marker to study (Fargotstein,2018)

Mismatch Negativity:

Mismatch negativity (MMN) is an evoked potential measured by scalp electroencephalography (EEG) electrodes generated in response to oddball stimuli (Image 1). A reduction in the absolute amplitude of MMN is another phenotype seen in SCZ that will be evaluated in this study. Persons with SCZ show defects in generating an enhanced response to the oddball stimuli in the MMN paradigm. MMN has been previously used to predict the conversion to psychosis in populations at clinical high risk for SCZ (Mathalon, 2016). MMN is also linked to cognitive impairments, which are seen in patients with 22q11.2 DS.

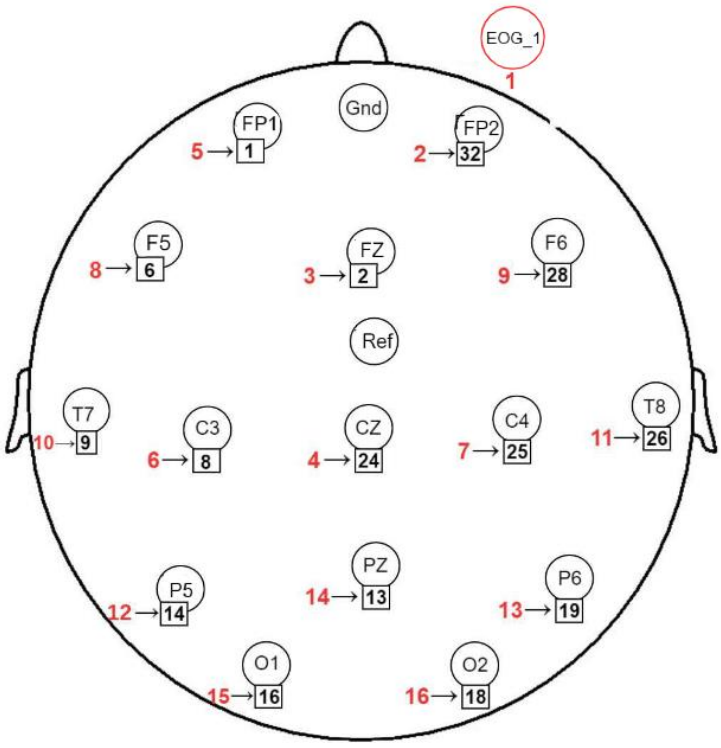

Image 1:

EEG electrode cap that the subject wears with the electrode placement locations for measuring MMN.

Cognitive Measures and Sensorimotor Skills:

Sensorimotor skills will be assessed through a simple finger tapping task (FTT), reaction time latency to a visual stimulus (RTT), and target detection during a visual oddball task. Clinical measures for each subject will be observed through The Structured Interview for Psychosis-Risk Syndromes (SIPS). Cognitive and sensorimotor measures will be compared to psychiatric symptom severity in the hopes of finding an association between the two.

WCST:

The Wisconsin Card Sorting Test is a simple computer game which asks the participants to match a given card to a row of four cards at the top of the screen. The card will display a certain number of the same of shapes with the same color, and the goal is to match that card with one of the four at the top based on the detail the computer wants. For example, if you are given a card with three red triangles and the game wants you to match that card based on the number of shapes on the card; you should match that card with one of the four at the top that has three shapes on it. After a few trials, the game will switch the detail it wants the user to match based on, and it is up to the participant to correctly pick up on the new trend. A correct response will be a change in the answer that accurately reflects the new pattern, and an incorrect is a perseverative error, in which the subject continues to use the prior pattern that is now incorrect to answer.

FTT:

For the FTT test, participants are asked to tap on a metal lever as fast as possible. This lever is attached to a wooden board and counter which counts how many time the participants tap the counter causing it to go down and touch the board and come all the back to starting position. There will be six trials on each hand, and the trials will be averaged and recorded.

RTT:

During the RTT test, a block box will appear on the screen, and the participant needs to hit a button with their right pointer finger as fast as they can in response to the appearance of the black box. Each participant gets five practice attempts before the actual trials begin.

SIPS:

The Structured Interview of Psychosis-Risk Syndromes is an interview conducted by a trained professional used to diagnose individuals with a high risk for developing SCZ or having an initial episode or prodromal symptoms. Patients deemed at clinical high risk by the SIPS have a 20% to 40% chance of developing SCZ within two to three years, making the SIPS a highly useful test for clinicians.

Statistics:

All data were stored on Redcap and Microsoft Access, and The Statistical Package for Social Science (SPSS) was used for all statistical analysis and modeling. Univariate analysis of variance (ANOVA) tests was used to quantify the significance in correlations between the two groups and the many variables tested. Each subject's age, race, and socioeconomic status (SES) were accounted for during these calculations. For SPSS reasons, socioeconomic status was coded as two groups, one and two. For SES, one was given to the group of participants making less than $35,000 a year, and two represented the group that makes more than $35,000 a year. For

education, we listed the years of education in order from least to greatest in order to find the median. The median was made the cutoff and the data was the split into two groups. The median was bachelor's degree, so our first group consisted of those with a bachelor's degree and lower, and the second group was all individuals with a master's or doctorate degree. Significant results were modeled with boxplots that were made using SPSS.

I hypothesized that 22q11.2DS patients will have increased startle latency and impaired MMN responses. 22q11.2DS patients will have increased error rates from the WCST, and 22q11.2DS patients will have performed worse on the sensorimotor tasks than healthy controls. 22q11.2DS patients will also show impairments in speed of target detection compared to healthy controls. Cognitive and sensorimotor measures will also be associated with the severity of clinical symptoms.

Results:

Tables 1A-D display the demographic makeup of each of the two groups, HC and 22q11.2 DS subjects: 52 total subjects; 21 22q11DS (average age 28) and 31 HC (average age 33; Table 1). The 22q11 group was made up of nine males and 12 females; the healthy controls were made up of 17 females and 14 males (Table 1A). For SES, 20 subjects did not list their yearly income, so only 32 subjects were included in this table. For both groups, there was almost an even split between those making above $35,000 and those making below (Table 1B). For education, many 22q11DS subjects did not obtain a bachelor's degree, and many for healthy controls obtained bachelors, masters, and doctorates degrees. According to table 1a, there were no significant differences between the two groups in SES ($F(1,1)= 1.098, .303$), age ($F(1,1)= 1.701, .198$), and sex ($F(1,1)= .701, .406$). However, there was a significant and expected difference between groups for levels of education ($F(1,1)= 8.504, .005$).

Table 2 displays the results from the cognitive, psychophysiological, and sensorimotor tests performed in this study. Unsurprisingly, the two groups differed on the prevalence of Positive and Negative symptoms of SCZ determined in the SIPS (P values <0.05). The two groups did not differ in the dominant hand FTT test or the non-dominant hand: both p-values were just above 0.05. Neither WCST errors nor perseverative responses were statistically significant between the two groups (P values > 0.05). Surprisingly, both the 22q subjects and healthy controls performed similarly on the RTT test (P value >0.05). The 22q subjects differed from healthy controls during the MMN oddball experiment when frequency and both duration and frequency of the stimulus were different (P value <0.05). However, when just the duration was altered neither group significantly differed from one another.

Figures 1 and 2 are boxplots that portray the relationship between group and SIPS performance. Figure 3 is a waveform of the MMN testing; that shows the difference between magnitude responses to typical stimuli and magnitude of responses to deviant stimuli. The absolute magnitude of responses to deviant stimuli were smaller in the 22q11.2DS group.

Discussion:

To our knowledge, few previous studies have evaluated the ASR or MMN in the 22q11.2DS population. MMN is also highly dependent on glutamatergic signaling which was studied in our lab through hiPSC-derived neurons, and this has also not been studied well in the 22q11.2DS population. This aspect of the study is still being conducted and being analyzed; however, we expect that hiPSC-derived neurons from the 22q11.2DS population will have impaired synaptic formation and neuronal transmission compared to the healthy population.

Demographics:

Firstly, our data show that the 22q11.2DS population and healthy controls only differed demographically on education level (Table 1D). This result is not surprising given the clear cognitive impairments seen in the 22q11.2DS population. However, it was surprising to see the lack of a significant difference between the populations for SES; however, many individuals did not report their yearly incomes. This statistic was highly affected by the lack of data for twenty individuals. Many 22q11.2DS individuals are unemployed or rely on family income, so it was expected that the 22q11.2DS sample would have lower SES than HC.

RTT:

It was quite interesting to see no significant differences between healthy controls and individuals with 22q11.2DS in the RTT. Individuals with schizophrenia have been shown to possess many cognitive impairments, especially in detecting visual stimuli as a result of impairments in the ventral attentional network (Wynn, 2015). Our reported lack of differences suggests that the 22q11.2DS population possesses an intact and functional attentional network. However, the cognitive deficits seen in the 22q11.2DS population make this result quite interesting and thought provoking.

FTT:

The finger tapping results were slightly above the significance threshold of $p < 0.05$ rendering them insignificant according to our pre-determined threshold (Table 2). It is possible that additional subjects would render this result statistically significant. Individuals with schizophrenia and individuals with 22q11.2DS show motor deficiencies, so it would be expected for there to be a statistical significance between the two groups.

WCST:

The lack of a statistically significant in the WCST tests between groups is also extremely interesting considering the known impairments in executive function in SCZ patients performing this task (Goldberg, 2002; Davis). Prior studies suggested the impairment in working memory and information processing that is seen in those with SCZ contributed to the worse performance on WCST. These results are further intriguing considering that our 22q11.2DS individuals also performed various tests on the Weschler Adult Intelligence Scale (WASI) and the Matrix Cognitive Battery (MCCB), and the results showed significant impairments even in the working memory of our 22q11.2DS subjects. Ceonsidering our subject's performances on the WASI and MCCB, we expected to see a difference in performance on the WCST as well. It is possible that increasing the number of subjects would render this result statistically significant.

SIPS:

Unsurprisingly, the 22q11.2DS subjects displayed higher levels of positive and negative symptoms of schizophrenia than our healthy controls. Positive symptoms are symptoms whose presence is abnormal. These include hallucinations, delusional thinking, incoherent speech, and disorganized behavior. Hallucinations can involve any sense but are most commonly auditory or visual (Montagnese, 2021). However, as dopaminergic transmission slows with age, so do the positive symptoms of schizophrenia. Negative symptoms include lack of motivation, lack of

emotional expression, apathy, and the lack of pleasure. These symptoms are hypothesized to result from abnormalities in the transmission and processing of dopamine, which is responsible for the main reward pathway in the brain (Schultz, 2013; Kesby, 2018). Our results gathered from the SIPS suggest that the 22q11.2DS population exhibit abnormalities in dopaminergic transmission, which contributes to the prevalence of both positive and negative symptoms of schizophrenia.

ASR:

Prolonged startle latency has been linked to patients suffering from schizophrenia, and latency is roughly 90% heritable and can predict the conversion to full SCZ (Hasenkamp et al. 2010). The North American Prodrome Longitudinal Study (NAPLS) found a significant relationship between slowing of startle latency and conversion to psychosis in prodromal subjects (Cadenhead et al. 2020), so we were expecting to see slower latency in 22q11.2DS subjects given their worse performance on the MCCB. However, we observed little to no differences between the 22q11.2DS subjects and the healthy controls, despite the 22q11.2DS subject's worse performance on our MCCB tests. However, after further analysis of the neuronal data and of ASR pre-pulse inhibition data when the study is completed, we hope to find observable differences between the groups for the ASR latency. This would indicated slower neuronal transmission and impaired cognition. However, currently our data suggests that our 22q11.2DS subjects have intact speed of neuronal transmission as indexed by ASR latency.

MMN:

Individuals suffering from SCZ have impaired responses to the oddball stimuli in MMN tests, and this result was observed in the 22q11.2DS sample when the frequency and the frequency + duration deviated from the norm (Figure 3). 22q11DS subjects displayed a higher MMN response during frequency deviant and double deviant trials. (Figure 3). These results could be

the result of a variety of mechanisms: NMDA signaling dysfunction that will be assessed in the hiPSC- derived neruons testing, grey matter abnormalities in cortical and subcortical auditory areas (Cantonas, 2021), or other differences in the auditory processing areas of the brain.

Significance and Future Directions:

In conclusion, it is possible we will observe more significant differences with the addition of more subjects; we still have about 50 more subjects to test before completion. With the addition of more subjects' differences might emerge in FTT that could suggest motor function impairment in 22q11.2DS individuals. With the completion and subsequent analysis of our stem cell-derived neuronal data, possible abnormalities in neuronal transmission speeds and other neuronal phenotypes could occur that would show similarities between our 22q11.2DS sample and patients with SCZ. The neuronal results could also answer questions as to what exactly is contributing to the MMN impairments in our 22q11DS subjects. Future studies could use brain scans to try and find observable differences between the brains of 22q11DS patients, SCZ patients, and healthy controls. We would predict that 22q11DS subjects would have less grey matter volume in the frontal lobe and diminished volume the hippocampus. Understanding the mechanisms that contribute to the development and onset of SCZ in the normal population and in the 22q11.2DS population might lead to the development of novel treatment targets. Future research should aim to develop personalized treatment for the many phenotypes of schizophrenia and related disorders. However, further data, especially from the hiPSC- derived neurons should be collected before drawing these conclusions.

Tables

Table 1: Demographic information by group

	22q11.2DS (n=21)	CON (n=31)
Age (years, mean ± SD)[a]	28 ± 10	33 ± 9
Sex (# of subjetcs)[b]		
Male	12	14
Female	9	17
Race (# of subjects)[c]		
African American	5	3
Caucasian	13	18
Other	2	10
Refused to answer	1	0
SES (# of subjetcs)[d]		
1	9	7
2	7	9
Education (# of subjects)[e]		
1	17	16
2	2	15

a: Age between groups: (F(1,29)= 1.701, P= 0.198)
b: Sex between groups: (F(1,29)= .701, P= 0.406)
c: SES between groups (1= >$35,000, 2= <$35,000): (F(1,29)= 1.098, P= 0.303)
d: Race between groups: (F(1,29)= .617, P= 0.437)
e: Education between groups: (F(1,29)= 8.504, P= 0.005)

Table 2

Table 2: Univariate analysis of Test Measures

	F-value	Significance	R2
RTT	0.143	0.709	0.031 (.171)
Nondominant FT	3.947	0.058	0.279 (.129)
Dominant FT	3.669	0.067	0.297 (.151)
SIPS Positive	5.370	0.029*	0.315 (.178)
SIPS Negative	20.916	<0.001*	0.554 (.465)
WCST Perseverative Errors	2.691	0.144	0.182 (.011)
WCST Perseverative Responses	4.012	0.057	0.263 (.109)
Frequency Deviant	5.241	0.030*	0.167 (.044)
Duration Deviant	2.797	0.106	0.197 (.078)
Frequency and Duration Deviant	7.813	0.009*	0.263 (.154)
ASR Amplitude	1.100	0.305	0.192 (.023)
Startle Latency	0.506	0.481	0.116 (.037)

* represents statisticial significance ($p < .05$)

Figures

Figure 1

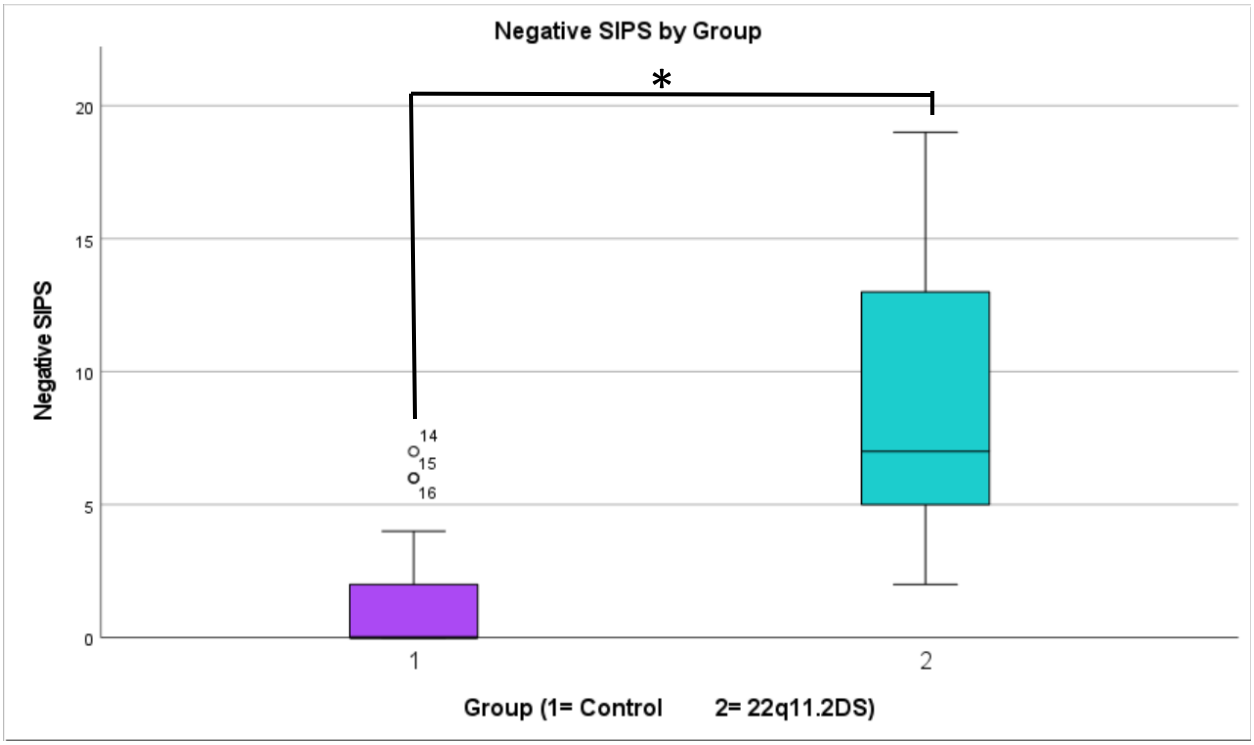

FIGURE 1: Comparison of rates of negative symptoms between 22q11.2DS patients and healthy controls determined by the SIPS. Group one (purple) represents the healthy controls, and group two (teal) represents the 22q11DS patients. As indicated by the boxplots, 22q11.2DS patients exhibited higher rates of negative symptoms determined by the SIPS. (* indicates statistically significant difference between groups, $p < .05$)

Figure 2

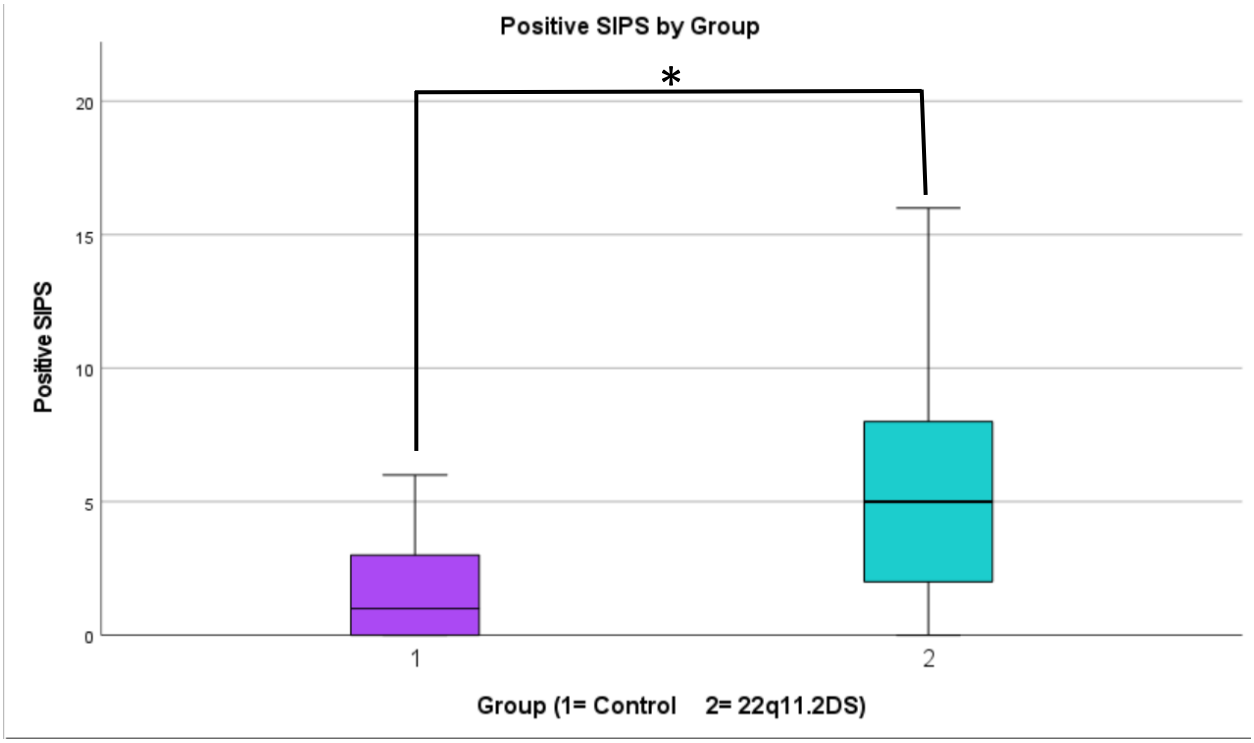

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Figure 3

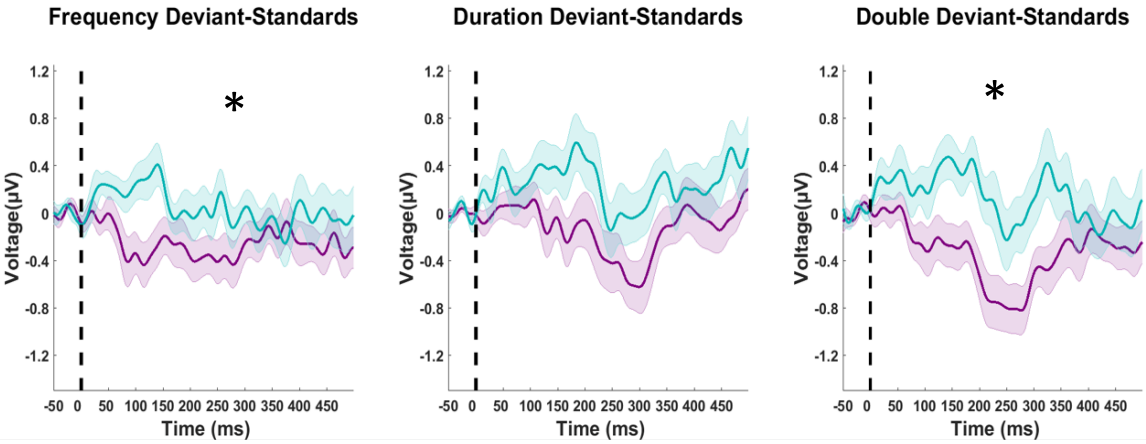

FIGURE 3: Comparison of MMN results between 22q11.2DS patients and healthy controls depicted in a Waveform graph. The difference wave for each group was gathered by subtracting the typical stimulus evoked response potential from the deviant stimulus evoked response potential. Teal wave represents the 22q11.2DS patients, and purple represents the healthy controls. 22q11.2DS patients showed higher MMN response to frequency and doubled deviant trials. (* indicates statistically significant difference between groups, $p < .05$)

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