Potential Role of Cortisol in Social and Memory Impairments in Individuals with 22q11.2 Deletion Syndrome

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Abstract

Keywords

- neurodevelopmental disorder
- cortisol
- 22q.11.2 deletion syndrome

22q11.2 Deletion syndrome is a genetic disorder characterized by physiological and psychological symptoms. This study investigated the role of cortisol on the social and cognitive impairments in children with 22q11.2. A total of 11 children with 22q11.2 were assessed for baseline cortisol levels and received broad neuropsychological testing. Results were compared with 11 controls. Children with 22q11.2 had significantly higher cortisol levels. A significant negative correlation was observed between the general memory and attention/concentration indices of the Wide Range Assessment of Memory and Learning, 2nd edition and cortisol concentrations in the control population. These data provide evidence of a possible causal mechanism that underlies social impairments in stress disorders.

Introduction

22q11.2 deletion syndrome is a genetic disorder that has several physiological and psychological symptoms. It has a prevalence rate of 1/4,300 to 7,000 and is commonly associated with learning disability and mild mental retardation in this population.^{1–3} Though the physiological symptoms associated with 22q11.2 deletion syndrome have been thoroughly studied, there is much to be understood with regard to the psychological features of the disorder. In particular, the neurochemical substrates underlying many of the social impairments expressed in these individuals have yet to be explored. Further examination of the neural substrates of social functioning in this population may provide insight into the brain–behavior relationships of social cognition.

Psychiatric Symptoms of 22q11.2 Deletion Syndrome throughout the Lifespan

In addition to many physical disorders that are observed in individuals with 22q11.2 deletion syndrome, there are nu-

merous comorbid psychiatric disorders.^{4–10} Specifically, children with 22q11.2 deletion syndrome present with generalized anxiety disorder, separation anxiety disorder, obsessive compulsive disorder, and specific phobias. Affective disorders are also often comorbid with 22q11.2 deletion syndrome.^{4,6} Bipolar disorder was found in 66% of children with 22q11.2 deletion syndrome who demonstrated affective symptomatology.

Adults with 22q11.2 deletion syndrome have much more severe, persistent anxiety than that observed in children with 22q11.2 deletion syndrome.¹¹ In addition, approximately 32% of individuals with 22q11.2 deletion syndrome will develop schizophrenia or other psychotic disorders during late adolescence or early adulthood.

Cognitive Deficits and their Neurological Correlates in Patients with VCFS

In addition to the numerous psychiatric illnesses associated with 22q11.2 deletion syndrome, there are multiple cognitive

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impairments of note. For example, individuals with 22q11.2 deletion syndrome frequently have a borderline intelligent quotient (IQ).¹² Approximately 25 to 40% have an IQ below 70.

Furthermore, deficits in attention, cognitive flexibility, and working memory are common.¹³ Many of these deficits have been associated with impaired executive network efficiency.¹⁴

Individuals with 22q11.2 deletion syndrome also show impairment in visuospatial and numerical abilities. These impairments have been associated with structural deficits of the parietal lobe.^{2,15} For example, increased activation of the left supramarginal gyrus was noted as a function of computational difficulty in individuals with 22q11.2.

In addition to the aforementioned nonverbal memory deficits observed in individuals with VCFS, this population also exhibits some verbal working memory deficits.¹⁶ On tests of verbal working memory, children with VCFS performed significantly worse than their sibling counterparts.

Social Impairments Observed in Individuals with 22q11.2 Deletion Syndrome

Recent research has identified several social deficits that commonly occur in individuals with 22q11.2 deletion syndrome. One such social deficit is impaired social communication. Interestingly, individuals with 22q11.2 deletion syndrome develop normal communication skills throughout the first 2 years of life, but then show significant delays acquiring the ability to use short phrases and sentences.

Another social deficit that may emerge as a result of these communication issues is extreme shyness and withdrawal.⁵ Swillen et al¹⁷ administered the child behavior checklist (CBCL) to both individuals with 22q11.2 deletion syndrome and individuals with speech pathology and learning impairments. They found that individuals with 22q11.2 deletion syndrome exhibited significantly more withdrawal behavior. One of the social deficits that may result from the shyness and social withdrawal is a failure to initiate interactions.¹⁸ In their case study describing the language, speech, and psychological features of five individuals with 22q11.2, Eliez et al,² noted a significant deficit in the number of attempts made to interact.

Further contributing to deficits in social functioning are impairments in processing facial expressions.¹⁹ Individuals with 22q11.2 deletion syndrome perform significantly worse on facial emotional processing tasks compared with age- and IQ-matched controls.

Finally, individuals with 22q11.2 deletion syndrome show affective abnormalities that interfere with social relations. Individuals with 22q11.2 deletion syndrome have been shown to have a flatter affect than normal controls during engagement in social interactions. Furthermore, their facial response tends to be expressionless during social engagements that usually facilitate both affective and facial responses.²⁰

Psychological Problems Associated with Long-Term Exposure to Glucocorticoids

There have been numerous psychological disorders mediated by or exacerbated by long-term exposure to stress. post-

traumatic stress disorder (PTSD), generalized anxiety disorder, and panic disorder have been associated with increased cortisol levels.^{21,22} The amygdala is a neurological structure directly implicated in anxiety and depression. Corticosteroids have been shown to increase the corticotropin-releasing hormone (CRH) mRNA expression at the central nucleus of the amygdala.²³ This expression increases activation in the amygdala, leading to a potentiation of the fear response and symptoms of anxiety. Thus, cortisol can affect the development of anxiolytic symptoms via promotion of CRH release in the central nucleus of the amygdala.

To conclude, increased cortisol levels may contribute significantly to the psychopathology and cognitive deficits observed in individuals with 22q11.2 deletion syndrome. To date, there have been no studies examining the direct impact of cortisol on psychopathology in this particular population. However, given evidence from other populations, it is reasonable to conclude that some of the observed short-term memory deficits, mood impairment, anxiety, and psychotic symptoms may be mediated or exacerbated by the presence of high baseline cortisol levels in individuals with VCFS.

Specific Social Deficits Related to Abnormal Cortisol Levels

As aforementioned, cortisol and the subsequent production of glucocorticoids has been implicated in anxiety,²¹ depression,²⁴ and social impairment²⁵ in related populations. To date, anomalous cortisol levels have not yet been demonstrated in this population but have been shown in children with autism spectrum disorder (ASD)^{26–28} and schizophrenia,^{29,30} two disorders commonly associated with 22q11.2 deletion syndrome. Specifically, in children with ASD, higher corticotropin levels were observed relative to control children suggesting a significant disruption in the hypothalamic–pituitary–adrenal axis.²⁷ Additionally, higher cortisol levels in children with ASD were associated with greater sensory sensitivity and social stress.²⁵ Finally, cortisol levels in children with ASD were correlated with parental attachment. Aberrant cortisol levels in children with ASD were related to poorer attachment ratings as measured by the strange situation procedure.²⁶ Moreover, the severity of autistic symptoms was also correlated with baseline cortisol levels. Thus, given what is known about this hormone in children with ASD, it is conceivable that cortisol may have both a direct or indirect impact on overall social competency in 22q11.2 deletion syndrome, a population that exhibits considerable social impairment.

Hypotheses

Specific aim 1 was to determine if there are differences between baseline cortisol levels in individuals with 22q11.2 deletion syndrome relative to controls. Given the role that cortisol plays in emotional processing and the experience of anxiety and the fact that children with 22q11.2 deletion syndrome have increased anxiety likely due to their neuronal architecture, cognitive interpretation of stressful events, and as they are less emotionally stable, it was hypothesized that individuals with 22q11.2 deletion syndrome would have a

significantly higher baseline cortisol levels relative to controls.

Specific aim 2 was to assess the relationships between cortisol levels and memory and social functioning in individuals with 22q11.2 deletion syndrome. Given the impact that elevated cortisol levels have on neurological structures supporting working memory, long-term memory, attention/concentration, and nonverbal memory storage, it was predicted that cortisol level would be negatively correlated with measures of cognitive performance in these domains. As a result of the significant anxiety observed in individuals with 22q11.2 deletion syndrome, it was hypothesized that the cortisol levels would be negatively correlated with measures of social competency and social functioning.

Methods

Participants

Subjects included 22 children (11 males and 11 females) aged 6 to 16 years. Of these 11 children (6 males and 5 females, mean age = 11.6 years) were individuals diagnosed with 22q11.2 deletion syndrome. The other 11 children (6 males and 5 females, mean age = 12.5 years) served as controls. The neurotypical children were all of average intellectual ability based on brief neuropsychological testing using a two subtest intelligence scale. Previous experiments using cortisol analysis have demonstrated large effect sizes ($d = 0.66$ to 0.85), justifying the use of 20 subjects.^{31,32} Children with 22q11.2 deletion syndrome were recruited primarily through the 22q11.2 deletion syndrome network of support groups. Peer nomination and sibling controls were used to recruit neurotypical controls. A list of a group of local children of matching ages was generated. From this, a random sampling was taken.

Inclusion criterion for the current study included a 22q11.2 deletion syndrome diagnosis confirmed by fluorescence in situ hybridization and documented formal diagnosis of 22q11.2 by a hospital genetics department. Controls were matched with 22q11.2 deletion syndrome individuals on the variables of age and sex. Exclusion criteria for children with 22q11.2 deletion syndrome included the presence of pre- or perinatal pathology, head injury, or substance abuse. In controls, the exclusion criteria consisted of the presence of learning disabilities or other neurological insults. An informed consent was obtained from the parents of children with 22q11.2 deletion syndrome and controls upon the first consultation following a demographic interview.

Measures

Child Behavior Checklist

The CBCL is a standardized, parent-report measure of children's (ages 4–18 years) behavior problems and competencies. The problem portion of the measure consists of 118 specific problem items that compose 9 subscales. The competency portion of the measure contains 20 items that compose 3 subscales.

Adaptive Behaviors Assessment System, 2nd Edition

The Adaptive Behaviors Assessment System, 2nd edition (ABAS-II, parent form; ages 5–21 years) is a diagnostic assessment measuring adaptive behaviors associated with daily functioning in both domestic and external social environments. It consists of 232 items that compose 10 primary skill areas: communication, community use, functional academics, home living, health and safety, leisure, self-care, self-direction, social, and work.

Wide Range Assessment of Memory and Learning, 2nd Edition

The Wide Range Assessment of Memory and Learning, 2nd edition (WRAML-2) is a comprehensive assessment of memory and learning designed to assess memory abilities following traumatic brain injury, neurological insult, trauma, and other psychological issues. Generally, the WRAML assesses immediate and delayed recall, verbal memory, visual memory, and working memory. Primary indices include general memory, verbal memory, visual memory, and attention-concentration. These indices are composed of 17 subtests assessing different domains of cognitive functioning.

Revised Children's Manifest Anxiety Scale

The revised children's manifest anxiety scale (RCMAS) is widely used self-report measure designed to assess the degree and nature of anxiety in children and adolescents aged 6 to 19 years. This measure is administered through a series of 37 items to which the child answers "yes" or "no." The "yes" responses are considered descriptive of the child's feelings or actions, and are counted towards a total anxiety score comprised of four subscales. Because each "yes" answer adds up to the total anxiety score, a high score is indicative of a high level of anxiety in the child.

Design

The design of this experiment was a quasi-experimental study comparing two groups: A 22q11.2 deletion syndrome group and a control group on cortisol levels, neurocognitive functioning, and social competence. It was a between-groups design despite the fact that subjects were matched on certain characteristics. Individuals were assigned to groups based on the presence or absence of VCFS.

Procedures

Neuropsychological Procedures/Protocol

Neuropsychological testing was completed by a trained psychometrician at various testing locations. The children underwent the neuropsychological assessment in the late morning. Cortisol swabs were taken before the assessment at 11 AM to control for neurohormonal responses to testing conditions. Testing order of experimental measures was as follows: (1) WRAML-2; (2) CBCL; (3) ABAS-II; and (4) RCMAS-2. Total length of testing was approximately 2.5 hours, a time interval short enough to reduce the impact of fatigue on cognitive performance.

Cortisol Procedure

Cortisol samples were taken from children at about 11:00 AM. Eleven in the morning was selected due to the relative stability of cortisol flux at this time of the day.³³ Times earlier than 11 AM are more impacted by individual differences in the child's sleep-wake cycle and therefore can confound results.³⁴ Samples were acquired with a standard buccal swab using the passive, unstimulated collection method. Children were directed to tilt their head forward allowing the saliva to pool near their bottom lip. A swab intended for use with children 6 years or older was used to collect approximately 1 mL of saliva. The swab was placed in a collection vial made of polypropylene intended to preserve the molecular structure of the steroid. The sample was then marked with both a numerical and bar code identification tag and placed in an insulated container and kept below 7 to 10°C. Temperature was monitored throughout the process using a standard body thermometer.

Following the field collection process, the samples were shipped within 24 to 48 hours in their insulated containers to the Salimetrics laboratory (State College, Pennsylvania, United States) for salivary cortisol distribution analysis. Using the standard immunoassay saliva extraction procedure, the steroid, cortisol, was then chemically isolated and concentrations per volume calculated and reported.³⁵

Collection materials and vials were purchased from the Salimetrics laboratory. Cortisol samples were destroyed immediately following analysis to comply with personal health information regulations. Data were deidentified and password protected to comply with privacy regulations.

Analysis

Analysis methods for both cortisol concentrations and neuropsychological test data included standard descriptive techniques for continuous variables. Assumptions of normality were checked using standard techniques including tests for normality, skew, and kurtosis. Effect sizes were also calculated and reported.^{36–38}

Initial analysis included a between groups analysis of variance (ANOVA) to determine if there are any, baseline cortisol differences (µg/dL), neurocognitive differences, or social/adaptive differences between individuals with 22q11.2 deletion syndrome and controls. ANOVA was used to reduce α inflation.

To examine the behavioral ramifications of cortisol anomalies in individuals with 22q11.2 deletion syndrome, Pearson r correlations assessing the relationship between cortisol levels and specific subscales of the CBCL, ABAS-II, and the WRAML-2 were conducted. ▶ **Table 1** describes the specific analyses that were conducted to address the hypotheses in question and correlation results.

Results

This project examined the concentration of a specific stress hormone, cortisol, in individuals with 22q11.2 deletion syndrome and its impact on cognitive and social functioning in individuals with 22q11.2 deletion syndrome. To do this, saliva

Table 1 Summary of analyses and correlation results between cortisol level and subscales of the CBCL, ABAS-II, WRAML-2, and RCMA5-2

Subscale	Correlation between cortisol and psychological measures in VCFS patients
	r Value
CBCL	
Anxious/depressed	0.144
Social problems	0.169
Thought problems	−0.406
Social competency	−0.109
ABAS-II	
Socialization	0.563
Communication	−0.222
WRAML-2	
General memory	−0.342
Working memory	0.422
Attention/concentration	−0.516
RCMA5-2	
Social anxiety	0.563
Total anxiety	0.487

Abbreviations: ABAS-II, Adaptive Behaviors Assessment System, 2nd ed; CBCL, child behavior checklist; RCMA5-2, Revised Children's Manifest Anxiety Scale, 2nd ed; WRAML-2, the Wide Range Assessment of Memory and Learning, 2nd ed.

samples were obtained using the aforementioned analysis procedures and the cortisol concentration calculated. Next, the performance on neuropsychological memory and attention measures along with measures of social functioning in individuals with 22q11.2 deletion syndrome was compared with control subjects. Finally, the relationship between the steroid hormone and scores on specific cognitive and behavioral measures were examined in individuals with 22q11.2 deletion syndrome to determine the impact of cortisol on these domains of functioning. ▶ **Table 2** provides the mean cortisol concentration for each group and corresponding effect sizes for individuals with 22q11.2 deletion syndrome and controls. ▶ **Table 3** provides means and standard deviations for select subtests of the WRAML-2 in individuals with

Table 2 Mean volume (mL) and SD of cortisol in individuals with 22q11.2 and controls

Hormone	22q11.2		Controls		Effect size (d)
	M	SD	M	SD	
Cortisol	0.25354	0.21342	0.10408	0.05443	1.01

Abbreviations: M, mean volume; SD, standard deviation.
Note: Cortisol concentrations are in micrograms per deciliter (µg/dL). Effect size is calculated as Cohen "d."

Table 3 Mean index scores, SDs, and effect sizes for WRAML-2 indices in individuals with 22q11.2 and controls

WRAML-2 index	22q11.2		Controls		Effect size (d)
	M	SD	M	SD	
General memory	74.03	12.76	109.45	14.22	−2.74
Working memory	88.88	22.90	108.88	8.590	−1.70
Attention/concentration	79.63	13.269	101.83	16.573	−1.55

Abbreviations: M, mean index score; SD, standard deviation; WRAML-2, the Wide Range Assessment of Memory and Learning, 2nd ed.
 Note: Effect size is calculated as Cohen “d.”

22q11.2 deletion syndrome and controls. ►Table 4 summarizes mean scores of behavioral measures of functioning including the CBCL, ABAS-II, and RCMAS-2 in individuals with 22q11.2 deletion syndrome and controls.

Specific Aim 1

It was predicted that salivary cortisol concentrations would be higher in individuals with 22q11.2 deletion syndrome relative to controls. ►Fig. 1 displays the mean cortisol concentration in individuals with 22q11.2 deletion syndrome and controls. Results indicated that mean cortisol concentration was significantly larger in individuals with 22q11.2 deletion syndrome relative to controls, $F(1, 20) = 5.436$, $p < 0.05$.

Specific Aim 2

It was hypothesized that the cortisol level in individuals with 22q11.2 deletion syndrome would be significantly correlated with cognitive measures and measures of social and adaptive functioning. There were no significant correlations between cognitive measures and cortisol in individuals with 22q11.2 deletion syndrome. That said, a significant negative correlation

was observed between the general memory and attention/concentration indices of the WRAML-2 and cortisol concentrations in controls: $r^{11} = -0.778$, $p < 0.05$; $r^{11} = -0.618$, $p < 0.05$. ►Figs. 2 and 3 graphically depict the relationship between cortisol, the general memory index score, and the attention/concentration index score.

There were no significant correlations observed in individuals with 22q11.2 deletion syndrome on select subscales of the ABAS-2, CBCL, and RCMAS-2. That said, the level of cortisol in control individuals was negatively correlated to the social competency scale of the CBCL, $r^{11} = -0.639$, $p < 0.05$. ►Fig. 4 is a graphical representation of the correlation between cortisol concentration and the social competency subscale of the CBCL in controls.

Discussion

Children with 22q11.2 Deletion Syndrome Show Elevated Cortisol Levels

The hypothesis that individuals with 22q11.2 deletion syndrome would have elevated resting cortisol levels relative to controls was supported. Though this has been the first study

Table 4 Means and SDs for subscales of the CBCL, ABAS-II, and RCMAS in children with 22q11.2

Subscale	22q11.2		Controls		Effect size (d)
	M	SD	M	SD	
CBCL ^a					
Anxious/depressed	56.26	8.01	50.09	2.50	0.95
Social problems	57.13	8.57	50.54	0.687	1.14
Thought problems	58.82	8.91	52.00	3.06	1.07
Social competency	46.00	11.55	51.00	8.30	−0.52
ABAS-II ^b					
Socialization	100.69	19.73	112.81	10.52	−0.80
Communication	7.36	3.21	11.81	1.66	−1.83
RCMAS-2 ^c					
Social anxiety	49.78	11.20	46.72	8.93	0.33
Total anxiety	50.43	11.47	46.81	9.61	0.36

Abbreviations: CBCL, child behavior checklist; ABAS-II, Adaptive Behaviors Assessment System, 2nd ed; RCMAS-2, Revised Children's Manifest Anxiety Scale, 2nd ed; WRAML-2, the Wide Range Assessment of Memory and Learning, 2nd ed.

^aM = 50, SD = 10.

^bM = 100, SD = 15 for composite, M = 10, SD = 3 for individual scales.

^cM = 50, SD = 10.

Fig. 1 Mean cortisol concentrations ($\mu\text{g/dL}$) ($\pm\text{SE}$) for individuals with 22q11.2 ($n = 11$) and control individual ($n = 12$). SE, standard error.

to demonstrate this elevation in a population of individuals with 22q11.2 deletion syndrome, it has been observed in related populations.

It may be possible that children with 22q11.2 deletion syndrome have an overactive hypothalamic-pituitary-adrenal axis that leads to the oversecretion of cortisol during both stressful and nonstressful events. Select groups such as individuals who are predisposed to the development of PTSD and children with neurodevelopmental disorders such as ASD exhibit an elevated cortisol response when presented with minor-to-moderate stressors relative to control counterparts.³⁹

Increased cortisol levels may also be associated with difficulties regulating the feedback loop which maintains cortisol production. Hippocampal volume anomalies have been observed in this population.⁴⁰ It is possible that genetic, environmental, or combined influences on hippocampal

Fig. 2 Relationship between average cortisol concentration ($\mu\text{g/dL}$) and the general memory index score of the WRAML-2 in controls. WRAML-2, the Wide Range Assessment of Memory and Learning, 2nd ed.

Fig. 3 Relationship between average cortisol concentration ($\mu\text{g/dL}$) and the attention/concentration index score of the WRAML-2 in controls. WRAML-2, the Wide Range Assessment of Memory and Learning, 2nd ed.

functioning influence the resting levels of cortisol in this population. This is speculative at this juncture because to date no one has observed glucocorticoid receptor functioning in this population.

Children with 22q11.2 Deletion Syndrome Perform Significantly Poorer on Selected Tests of Memory and Learning

The hypothesis that children with 22q11.2 deletion syndrome would exhibit reduced cognitive abilities relative to control counterparts was supported. Specifically, children with 22q11.2 deletion syndrome exhibited poorer performance in general memory ability, attention, and concentration ability, and working memory ability. This finding is not surprising given the high rate of attention-deficit/hyperactivity disorder (ADHD) and learning disability observed in this population. Children with 22q11.2 deletion syndrome exhibit

Fig. 4 Relationship between average cortisol concentration ($\mu\text{g/dL}$) and the total competency subscale of the CBCL. CBCL, child behavior checklist.

an inattentive subtype of ADHD characterized by poor ability to focus and short attention span.

In addition to inattention and concentration deficits, individuals with 22q11.2 deletion syndrome in this study exhibited general memory deficits. These data are consistent with previous findings examining the cognitive profile of children with VCFS.^{17,41–44} It has been reported that the general memory deficits observed in this population relate to neuroanatomical and functional inefficiencies in bilateral hippocampus of children with 22q11.2 deletion syndrome. As previously stated, children with 22q11.2 deletion syndrome have decreased hippocampal volume.^{40,45} These volumetric anomalies have been correlated with decreased performance on tests of memory and learning relative to neurotypical children.⁴³

Working memory abilities were also found to be reduced in children with VCFS relative to controls. These data have also been reported and therefore the data reported in this study are consistent with previous findings.^{16,42,46–48} Working memory requires a combination of neurological structures working in concert. Specifically, working memory is supported by subregions of the frontal lobe and the parietal lobe.^{18,49}

It is unclear what the role of cortisol is in mediating cognitive deficits observed in this population. More research is necessary to determine whether elevated cortisol levels underlie some of the morphometric anomalies in children with 22q11.2 deletion syndrome.

The Relationship between Cortisol and Cognitive and Behavioral Measures of Functioning

The hypothesis that cortisol levels would be correlated with selected measures of cognitive functioning and social competence in individuals with 22q11.2 deletion syndrome was not supported. Though it is possible to conclude that cortisol may be unrelated to these cognitive and behavioral measures, drawing such a conclusion is premature given the relationships observed in the control group. In the control group, a significant negative correlation was observed between cortisol and social competence as measured by the CBCL. Additionally, a negative correlation was observed between cortisol and the attention/concentration subscale of the WRAML-2. Thus, in controls, aspects of neurocognitive functioning are correlated with resting cortisol levels. This may imply that in children with 22q11.2 deletion syndrome another physiological or neuroanatomical mechanism may be influencing the strength and direction of the relationship between cortisol and neurocognitive and behavioral measures or that the sample size in this study was insufficient to detect a subtle relationship between cortisol and performance on neurocognitive tests.

Possible Treatment Implications

Given what is observed in neurotypical children regarding the relationship between cortisol level, cognitive performance, and social competence, this study has some relevant treatment implications. Reduction of cortisol level has been shown to improve mood impairment and cognitive function-

ing.⁵⁰ When used to treat bipolar disorder, mifepristone, an antiglucocorticoid drug, was effective in reducing hypercortisolemia. Following the reduction of glucocorticoids, verbal fluency, spatial recognition abilities, and working memory abilities improved significantly relative to a no treatment control group. In addition, mood symptoms were also reduced. To date, there have not been any published studies examining the impact of mifepristone on cognitive functioning and social competency in individuals with 22q11.2 deletion syndrome. Given the high rate of bipolar disorder in this population and the relative effectiveness of the drug to treat both mood and cognitive symptoms it may be a useful treatment in this population and further research is necessary to determine the efficacy and safety of the drug in symptom improvement in this population.

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