

How might stress contribute to increased risk for schizophrenia in children with chromosome 22q11.2 deletion syndrome?

Elliott A. Beaton · Tony J. Simon

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Abstract The most common human microdeletion occurs at chromosome 22q11.2. The associated syndrome (22q11.2DS) has a complex and variable phenotype with a high risk of schizophrenia. While the role of stress in the etiopathology of schizophrenia has been under investigation for over 30 years (Walker et al. 2008), the stress–diathesis model has yet to be investigated in children with 22q11.2DS. Children with 22q11.2DS face serious medical, behavioral, and socioemotional challenges from infancy into adulthood. Chronic stress elevates glucocorticoids, decreases immunocompetence, negatively impacts brain development and function, and is associated with psychiatric illness in adulthood. Drawing knowledge from the extant and well-developed anxiety and stress literature will provide invaluable insight into the complex etiopathology of schizophrenia in people with 22q11.2DS while suggesting possible early interventions. Childhood anxiety is treatable and stress coping skills can be developed thereby improving quality of life in the short-term and potentially mitigating the risk of developing psychosis.

Keywords Allostatic load · Children · Cortisol · Developmental disorder · Genotype · Hypothalamic–pituitary–adrenal axis (HPA axis) · Socioemotional development · Schizophrenia · Stress–diathesis · Velo-cardio-facial syndrome (VCFS)

Introduction

Chromosome 22q11.2 deletion syndrome (22q11.2DS) results from a one point 5 to three-megabase deletion on the q11 band of chromosome 22 (Driscoll et al. 1993; Scambler 2000; Botto et al. 2003). Alongside physical, cognitive, and socioemotional impairments, 22q11.2DS confers a 25- to 30-fold increased risk for schizophrenia over the general population. Only the rare occurrence of having two parents or a monozygotic twin with schizophrenia confers a greater risk. In patients with a diagnosis of schizophrenia, there is a 20- to 80-fold elevated prevalence of the deletion compared to the general population (Murphy 2002; Bassett et al. 2003). There are no clear clinical phenotypic differences between schizophrenic patients with and without 22q11.2DS (Bassett et al. 2003; Arinami 2006). Early identification makes 22q11.2DS an ideal research population for prospectively investigating risk and protective factors for schizophrenia.

Recently, Karayiorgou and colleagues (2010) highlighted the complexity of the pathogenesis and pathophysiology of 22q11.2DS, especially as it relates to predicting psychosis and further indicating the need for longitudinal studies. The single prospective study of children with 22q11.2DS (Gothelf et al. 2007) found that baseline anxiety and mood, lower verbal IQ, and psychotic symptoms, along with catechol-*O*-methyltransferase (COMT) genotype, predicted young adult onset and severity of psychosis. Somewhat surprisingly, given the richly developed human and animal literature on the effects of anxiety and stress on brain development and risk of neuropsychiatric disease (Bremner et al. 1997; Heim and Nemeroff 2001; McEwen 2003; Marco et al. 2010) and schizophrenia in particular (Read et al. 2005; Morgan and Fisher 2007; Walker et al. 2008; Freeman and Fowler 2009), there has been no

E. A. Beaton (✉) · T. J. Simon
Department of Psychiatry and Behavioral Sciences
and the M.I.N.D. Institute, University of California Davis,
2825 50th Street,
Sacramento, CA 95817, USA
e-mail: eabeaton@ucdavis.edu

T. J. Simon
e-mail: tjsimon@ucdavis.edu

focused examination of physiological and psychological sequelae of stress in this population.

Children with 22q11.2DS have real and ongoing physiological and psychological stressors beyond those of typically developing children. Anxiety is common in children with 22q11.2DS and likely results from a multivariate interaction of genetically derived temperament (Swillen et al. 1999; Jabbi et al. 2007; Michaelovsky et al. 2008), early traumatic experiences (e.g., cardiac surgery; Mahle et al. 2003), and the day-to-day challenges (medical and otherwise) associated with the syndrome. Anxiety is a cognitive manifestation of fear and can elicit a robust sympathetic stress response (de Catanzaro 1999) that can deplete physiological coping resources and exacerbate existing cognitive and socioemotional impairments in a reciprocal fashion.

Genetic copy number and genotypic variations in the deleted region evidently contribute to the etiopathogenesis of schizophrenia and also predict susceptibility to stress and anxiety in populations without 22q11.2DS (Stein et al. 2005; Roussos et al. 2009). Furthermore, chronically elevated glucocorticoid release as part of the stress response can negatively affect brain development in humans and animal models (McEwen 2007). Therefore, we suggest that several aspects of 22q11.2DS may both contribute to and be exacerbated by the pathological sequelae of coping with long-term, and often unpredictable, stressors. This is not a simple unidirectional relationship. The physiological effects of chronic stress in children with 22q11.2DS may trigger the, as yet, undefined diathesis leading to schizophrenia. However, we do not claim that anxiety or stress causes schizophrenia in children with 22q11.2DS. There are many groups of people with developmental disabilities coping with serious stressors related to those disabilities that do not possess the same risk of developing schizophrenia as children with 22q11.2DS. Conversely, there are populations with intellectual and developmental disabilities such as multiple complex developmental disorder at risk for psychosis (Sprong et al. 2008) but again, not to the same degree as children with 22q11.2DS.

The microdeletion imparts a developmental risk that has not yet been clearly elucidated and is neither necessary nor sufficient for developing schizophrenia. The evidence that approximately 2% of patients with schizophrenia were found to have a chromosome 22q11.2 deletion (Bassett and Chow 1999) and that approximately two thirds of children with the deletion will not develop schizophrenia highlights the need for further research elucidating not just risk factors but also factors that protect against psychopathology (Baker and Skuse 2005; Stoddard et al. 2010).

We suggest that a high preponderance of serious negative life events throughout development in combination with greater susceptibility to stress and anxiety, and

poorer coping skills contribute to risk of schizophrenia in people with 22q11.2DS. Below, we review relevant data and suggest how the anxiety and stress literature can increase our understanding of the risk factors that lead to schizophrenia in one third of children with 22q11.2DS.

Stressors associated with 22q11.2DS

Traumatic early life experiences can shape the physiological stress response over development and are predictive of atypical hypothalamic–pituitary–adrenal (HPA) axis activation and neuroendocrine dysregulation (Plotsky and Meaney 1993; Heim and Nemeroff 2001; Turner-Cobb 2005; Elzinga et al. 2008) and psychosis (Freeman and Fowler 2009) in adulthood. From an early age, children with 22q11.2DS often have extensive and serious medical issues. Pathophysiological manifestations of the deletion can include a variety of cardiac and palatal anomalies, immunological deficiencies, and metabolic and endocrine disorders (Bassett et al. 2005; Shprintzen 2008). Congenital cardiac defects can impact myocardial and cerebral development (Carotti et al. 2008; Rudolph 2010), and serious variants, including tetralogy of Fallot, require very complicated, early surgical intervention. These occur in 49–83% of cases (Kobrynski and Sullivan 2007). Childhood bacterial and viral infections are common in 22q11.2DS, especially in those with defective or even absent thymus resulting in immunodeficiency and disordered T cell development (McLean-Tooke et al. 2007). In infancy, breastfeeding can be impacted with poor suckling and nasal regurgitation owing to malformations of the palate resulting in feeding complications that can extend into childhood (Cooper-Brown et al. 2008).

The cognitive profile of children with 22q11.2DS has been characterized as uneven with a mean full scale IQ between 70 and 85 (Woodin et al. 2001). Delays and impairments in language comprehension and production, visuospatial and numerical processing (Bearden et al. 2001; Simon et al. 2005a), attention, and executive function (Dufour et al. 2008) are typical in this population. As the child with 22q11.2DS ages and enters the school system, his or her cognitive and social impairments become more apparent in the context of increasing social and academic expectations. In the socioemotional arena, children with 22q11.2DS often have social and communication impairments and are more likely to be anxious, shy, and socially withdrawn (Swillen et al. 2001). They are more likely to be diagnosed with mood disorders, attention deficit hyperactivity disorder (ADHD), and obsessive–compulsive disorder (OCD) (Arnold et al. 2001), all of which further impact their ability to perform well in school and develop positive reciprocal relationships with peers

their own age. Bullying is not uncommon in children with learning difficulties (Burkhardt 2005), and this often induces potent sympathetic nervous responses that may contribute to dysregulation of the HPA axis in those children who are bullied (Vaillancourt et al. 2008).

Parental coping ability and access to socioemotional and financial support is also a critical component of a child's ecology and can serve as protective factors or further contribute to stress and anxiety. Parents of children with 22q11.2DS face numerous challenges, including medical care and costs, educational difficulties, and general uncertainty about the future. Parents vary in their coping abilities based on social and financial support. Parents report feeling anxious in response to behavior problems in their infants with 22q11.2DS (Briegel et al. 2007). They also worry that older children will develop a psychotic illness (Hercher and Bruenner 2008). Parental anxiety can increase children's stress levels and positively correlates with increased illness in typical children (Wyman et al. 2007; Caserta et al. 2008) likely owing to stress-induced suppression of the immune response (Webster Marketon and Glaser 2008).

Stress, allostatic load, and the HPA axis

Allostatic load is the physiological cost of maintaining homeostasis when faced with severe or chronic stress. Allostasis can occur via physiological (e.g., cortisol release or blood pressure elevation) or behavioral (e.g., avoiding stress-inducing stimuli) mechanisms that are elicited in response to real or perceived challenges. While modulated by individual differences in genotype, experience, and environment, allostatic load can increase over time to the point of overload and exhaustion. Allostatic overload exhausts coping resources and overexposes the organism to the hormonal, immunological, and neural mediators released via chronic activation and dysregulation of the HPA axis. Allostatic overload can also manifest as an inability to habituate to stressors, a failure to inhibit the stress response when not needed or as the lack of an effective stress response when one is truly needed (McEwen 2007).

The HPA axis is a neural and glandular system that mediates physiological and behavioral responses to stressors, including the release of glucocorticoids (GC). The HPA axis is the most intensely investigated "stress response" system and is known to play a critical role in effectively coping with threat. In response to physical or psychological stressors, corticotrophin releasing hormone is secreted from the anterior part of the periventricular nucleus of the hypothalamus, which in turn stimulates adrenocorticotrophin releasing hormone (ACTH) from the anterior pituitary. This stimulates the release of androgenic steroids, mineralocorticoids, and GCs from the cortices of the

adrenal glands. Cortisol is the GC found in primates and GC and mineralocorticoid receptors are found throughout the periphery and brain. Cortisol release is regulated by ACTH via episodic release in a circadian rhythm and by negative feedback of cortisol on ACTH (Sapolsky 2003; Aron et al. 2004). Released as part of the stress response, cortisol liberates energy stores, increases cardiac output, and elevates mood and appetite while suppressing anabolic functions not immediately necessary to survival. However, chronic and unpredictable stressors can produce prolonged HPA axis activation with persistent elevated GC release (Sapolsky et al. 1986; Johnson et al. 1992). Chronic GC elevation is associated with pathologies, including depression and anxiety, immunological impairments, and nervous system damage, particularly involving the hippocampus in animals and humans (Sapolsky et al. 1990; Lange and Irle 2004; Yang et al. 2008). Chronic GC activation also increases prefrontal lobe vulnerability to inflammation (de Pablos et al. 2006), and higher baseline cortisol levels have been reported in patients with schizophrenia with a commensurate increase in negative symptoms during withdrawal from antipsychotic medications (Walker et al. 2008). Gene expression associated with upregulation of inflammatory processes have been found in the post-mortem brains of patients with schizophrenia (Saetre et al. 2007), suggesting a possible feed-forward mechanism that may contribute to atypical frontal lobe function reported in patients with schizophrenia (Weinberger et al. 2001) while possibly increasing stress sensitivity via a reduction in frontal modulation of limbic activity.

Stress and brain morphology

The correlation between genotype and phenotype can be low in 22q11.2DS, with even monozygotic twins demonstrating significant variability in symptom presentation (Goodship et al. 1995; Yamagishi et al. 1998; Hillebrand et al. 2000). However, similarities in brain morphometry exist between persons with 22q11.2DS and schizophrenia patients without 22q11.2DS (van Amelsvoort et al. 2001; Simon et al. 2005b; Kates et al. 2006). These neural anomalies are driven by both genetic and epigenetic factors and perhaps also in response to allostatic load. For example, children and adults with 22q11.2DS show hippocampal volume reductions (Debbané et al. 2006; DeBoer et al. 2007) similar to individuals with schizophrenia (Velakoulis and Pantelis 1996). Decreased dendritic arborization in the hippocampus may be accounted for by dysregulation of neural and synaptic genes as demonstrated in mouse models (Karayiorgou et al. 2010). However, chronic GC exposure is also associated with neuronal death, increased cytotoxic susceptibility to metabolic

challenges, reduced neurogenesis, decreased dendritic complexity and spine density in the hippocampi of animals (Sapolsky 1985, 1986; Sapolsky et al. 1985; Woolley et al. 1990; Mizoguchi et al. 1992; Margariños et al. 1996; McEwen 1999), and memory impairments and hippocampal atrophy in aged humans. It is possible that the lower hippocampal volumes reported in people with 22q11.2DS (e.g., Debbané et al. 2006; DeBoer et al. 2007) may not only reflect an atypical maturational process but also an atrophying process with functional implications as hippocampal volume is correlated with verbal IQ (Toulopooulou et al. 2004). In children with 22q11.2DS, a decline in verbal IQ along with COMT haplotype, elevated anxiety, and negative mood was predictive of psychotic symptom severity in young adulthood (Gothelf et al. 2005, 2007).

Overall brain volume is 8–11% smaller in children with 22q11.2DS than typically developing children and appears in an anterior to posterior pattern (Eliez et al. 2000; Kates et al. 2001; Simon et al. 2005b), which suggests a possible mechanism for emotional dysregulation in children with 22q11.2DS given the modulatory role of the frontal cortices on limbic activity and reactivity (Kinsbourne 1978; Fox et al. 1996; Davidson 2002). Abnormalities in frontal and limbic connectivity was recently demonstrated by Sigurdsson and colleagues (2010) with a *Df(16)A^{+/-}* mouse model of the human chromosome 22q11.2 deletion. These mice possess baseline dorsal hippocampal and medial prefrontal asynchrony associated with learning impairments on a working memory task. These findings mirror spatial working memory impairments reported in people with 22q11.2DS (Kates et al. 2007). Here too, GC activity may contribute to these observations. Stress and corticosterone (Diamond and Rose 1994; Alfarez et al. 2003) suppress long-term potentiation in *Cornu ammonis* 1 of the dorsal hippocampus and in the medial prefrontal cortex (mPFC; Maroun and Richter-Levin 2003) possibly contributing to abnormal connectivity between these regions.

Genotype and susceptibility to stress

The role of dopamine (DA) dysregulation in schizophrenia focused research on COMT haplogenotype in relation to psychopathology in 22q11.2DS (e.g., Dunham et al. 1992; Bassett et al. 2007; Gothelf et al. 2008) hypothesizing a modulation of schizophrenia susceptibility in individuals with and without 22q11.2DS (Arinami 2006; Bassett et al. 2007; Williams et al. 2007). Since 22q11.2DS results from a hemizygous deletion, probable reductions in messenger RNA and proteins produced by the potentially polymorphic genes in the unaffected chromosome may contribute to psychosis risk (Michaelovsky et al. 2008). COMT is an enzyme that inactivates catecholamines such as norepinephrine and dopamine. Lower enzymatic action on DA

may increase the likelihood of psychosis due to an overabundance of synaptic DA (Carlsson 1988; Dunham et al. 1992) and the low-activity allele has been correlated with ADHD, OCD, and schizophrenia incidence in some studies of 22q11.2DS (Bassett et al. 2007; Gothelf et al. 2007; Michaelovsky et al. 2008) and the general population (Shifman et al. 2002) but not in others (Murphy et al. 1999; Fan et al. 2005; Murphy and Scambler 2005) likely because of additional genetic and experiential variation (Craddock et al. 2006; Michaelovsky et al. 2008). Furthermore, while DA activity is enhanced by GCs in the prefrontal cortex (Mizoguchi et al. 2004), understanding of the complex relationship between CG and DA is still developing (Craenenbroeck et al. 2005).

Consider also that COMT appears to contribute to individual variability in stress sensitivity and coping. The COMT variant interacts with polymorphic variants of genes coding for monoamine oxidase A and serotonin transporters that increase susceptibility to major depression and anxiety via differences in ACTH secretion and HPA reactivity (Jabbi et al. 2007). When compared to carriers with the high-activity COMT allele, healthy adult carriers of the low-activity COMT allele show greater prefrontal cortical, amygdalar, and hippocampal activation in response to emotional tasks such as viewing faces displaying negative emotion (Smolka et al. 2005; Drabant et al. 2006). The low-activity COMT variant has also been linked to greater stress sensitivity, negative affect, and psychosis in response to an emotional task (van Winkel et al. 2008).

Recently, Gothelf and colleagues (2010) reported that age-related reductions in left dorsal prefrontal cortical (dPFC) gray matter volume predicted psychosis in adolescents and young adults with 22q11.2DS. Furthermore, those individuals with 22q11.2DS that possessed the low-activity COMT allele had greater reductions in dPFC than did those with the high-activity COMT allele. Other differences included decreased dorsal cingulum but increased volume of the mPFC, orbitofrontal cortex, and right amygdala. There is ample evidence that even relatively mild acute stress impairs PFC function and that protracted, intense, or uncontrollable stress reduces dendritic length, arbor complexity, and spine density in PFC and this may be moderated by COMT variant (see Arnsten 2009 for a review). Changes in prefrontal and limbic regions related to anxiety and negative life events have been reported in other populations of children both with and without neurodevelopmental disorders. For example, greater right amygdala volume is predictive of anxiety in children with autism (Juraneck et al. 2006). In another example, larger amygdala volumes in healthy children are associated with length of time spent in less-than-optimal rearing conditions such as an orphanage (Tottenham et al. 2010). Richert and colleagues (2006) found that children with post-traumatic stress disorder (PTSD) had lower total

gray matter, decreased dPFC, and increased middle-frontal and ventral PFC volumes when compared to children without PTSD. The authors suggest that this may indicate atypical brain development resulting in a premorbid risk factor that potentiates emotional dysregulation and fear or that changes in these regions reflect “use-dependent” prolonged activation of corticolimbic circuits following trauma. These are not mutually exclusive hypotheses and neither is the COMT genotype reported in Richert and colleagues’ (2006) study of PTSD in children. However, these examples highlight the need for further investigation in order to better understand the relationships between such processes given that at least one commonality between children with PTSD that are otherwise healthy and many children with 22q11.2DS is some experience of chronic stress.

COMT is not the only gene in the deleted region associated with stress reactivity and anxiety in populations without 22q11.2DS. The proline dehydrogenase (PRODH) gene in the 22q11.2 deleted region, regulates glutamate and γ -aminobutyric acid also making it a critical candidate in the etiopathology of schizophrenia in this population (Liu et al. 2002). In healthy adults, PRODH variant is associated with elevated prepulse inhibition, schizotypy, and greater anxiety (Roussos et al. 2009). Thus, in 22q11.2DS, PRODH haplotype might further contribute to stress sensitivity and anxiety via its actions on glutamate (Mathew et al. 2008).

Summary and future directions

The well-established body of anxiety and stress research has yet to be utilized to further clarify psychosis risk in 22q11.2DS, whose childhood population is, arguably, a near perfect model of early traumatic experience and chronic stress leading to an uncertain adulthood. These children have significant physical, cognitive, and socioemotional impairments they must overcome on a daily basis. We restate that we do not posit that stress or allostatic load causes schizophrenia in people with 22q11.2DS. Rather, that chronic stress and anxiety with associated physiological sequelae may modulate risk of psychosis. This is not a simplistic cause and effect relationship but rather a series of negative hits to an already challenged developing system. Susceptibility to stress may be modulated by allelic variation and phenotypic variability that may include serious medical issues such as major cardiac malformations early in development. Furthermore, variability in parental and community resources contribute to the complexity of understanding risk and resilience in these children.

To truly test the hypothesis that chronic and repeated stressors contribute to the risk of schizophrenia in people with 22q11.2DS will require longitudinal study from earliest diagnosis to adulthood. However, important longi-

tudinal inferences may be drawn from cross-sectional analyses and provide insight into the 22q11.2DS endophenotype at risk for schizophrenia. Furthermore, anxiety disorders in children are amenable to treatment, and stress coping skills can be developed (e.g., Kendall 1994). It should be possible to tailor interventions for children with 22q11.2DS that will have an impact not only on quality of life in the short-term, but also mitigate proposed stress-related risk of schizophrenia.

A detailed survey of all of the established methodologies for measuring stress and its physiological and developmental sequelae is beyond the scope of this article. There is evidently a great deal of work still to be done in order to tease apart the factors that affect psychiatric outcomes in 22q11.2DS. However, we suggest that a relatively simple first step would be to characterize stress reactivity in people with 22q11.2DS by measuring cortisol release at rest and in response to a mild stressor in relation to standardized measures of anxiety, mood, and life events. As of this writing, there are no published reports characterizing cortisol at rest or in reaction to any form of stressor in people with 22q11.2DS. As noted previously, cortisol modulates a wide variety of metabolic processes but in the context of a physical or emotional challenge, it is often thought of as a “stress” hormone as HPA-regulated sympathetic nervous system activation elevates cortisol levels. Other metabolic factors can be measured with cortisol such as dehydroepiandrosterone (DHEA). DHEA is an ACTH-regulated steroid that possesses anti-glucocorticoid properties (Kalimi et al. 1994) and the ratio of cortisol to DHEA may be a more nuanced metric of HPA axis tone, physical and psychological stress, resistance, and coping in children (Goodyer et al. 1998). These hormonal measures could also be accompanied by simple psychophysiological indicators of sympathetic nervous system activation such as galvanic skin response, heart rate, and blood pressure (see Schmidt and Segalowitz 2007 for a review) and these metrics could be tested against a variety of variables including COMT haplotype (van Winkel et al. 2008) and/or brain function (Bremner 2007) and structure (Sowell et al. 2004; Spinelli et al. 2009).

In summary, chronic stress and its sequelae may play a critical but as yet, uninvestigated bidirectional role in the physical, cognitive, and socioemotional development of children with 22q11.2DS and the likelihood of psychosis in adulthood.

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