HHS Public Access

Author manuscript

*J Psychiatr Res*. Author manuscript; available in PMC 2019 October 01.

Published in final edited form as:

*J Psychiatr Res*. 2019 July ; 114: 99–104. doi:10.1016/j.jpsychires.2019.04.011.

# Bullying and psychosis: The impact of chronic traumatic stress on psychosis risk in 22q11.2 deletion syndrome - a uniquely vulnerable population

**Danessa Mayo**[a,b,1], **Khalima A. Bolden**[a,*,1], **Tony J. Simon**[b], and **Tara A. Niendam**[a]

[a]Department of Psychiatry and Behavioral Sciences, Imaging Research Center, USA

[b]Medical Investigation of Neurodevelopmental Disorders (MIND) Institute, University of California, Davis, Sacramento, CA, USA

## Abstract

Bullying is an adverse childhood experience that is more common among youth with special needs and is associated with increased psychopathology throughout the lifespan. Individuals with chromosome 22q11.2 deletion syndrome (22q) represent one group of special needs youth who are at increased risk for bullying due to co-occurring genetically-mediated developmental, physical, and learning difficulties. Furthermore, individuals with 22q are at increased risk for developing psychotic disorders such as schizophrenia. However, there is a paucity of research exploring the impact of bullying on individuals with 22q and the possible impact this has on risk for psychosis in this population. To explore this relationship using existing research the goals of the review are: (i) to explore the nature of bullying among youth with special needs, and (ii) to discuss its potential role as a specific risk factor in the development of adverse outcomes, including psychosis symptoms. We reviewed the relationship between bullying and its short and long-term effects on the cognitive, social, and developmental functioning of typically developing individuals and those with special needs. We propose an interactive relationship between trauma, stress, and increased psychosis risk among youth with 22q with a history of bullying. The early childhood experience of trauma in the form of bullying promotes an altered developmental trajectory that may elevate the risk for maladaptive functioning and subsequent psychotic disorders, particularly in youth with genetic vulnerabilities. Therefore, we conclude the experience of bullying among individuals with 22q should be more closely examined.

### Keywords

22q11.2 deletion syndrome; DiGeorge syndrome; Bullying; Psychosis; Trauma; Chronic stress; Victimization

*Corresponding author. 4701 X Street, Sacramento, CA, 95817. USA. kbolden@ucdavis.edu (K.A. Bolden).

[1]Co-first authorship.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jpsychires.2019.04.011.

## 1. Introduction

The vulnerability-stress model for psychosis risk posits that interactions between endogenous and exogenous factors contribute to the development of psychosis spectrum disorders. This model hypothesizes that certain biological *vulnerabilities* (e.g., genetic predisposition, neurophysiological dysregulation, etc.) interact with environmental *stressors* (e.g., perinatal issues, adverse experiences, substance misuse, etc.) and lead to the emergence of psychosis symptoms (Nuechterlein and Dawson, 1984). When individuals possess a genetic or biological vulnerability to psychosis, they can only withstand a certain amount of environmental stressors; once this threshold of stress is surpassed, there is higher risk for the development of psychosis (Zubin and Spring 1977). From this perspective, the experience of trauma increases one's subjective stress and, therefore, leaves an individual with greater susceptibility to developing psychopathology.

One population has demonstrated unique genetic vulnerability to the development of psychosis: individuals with 22q11.2 deletion syndrome (22q; Stoddard et al., 2010). Chromosome 22q11.2 deletion syndrome (22q) results from the most common de novo microdeletion and occurs in approximately 1 in 2000–4000 live births (Botto et al., 2003; Grati et al., 2015; Shprintzen, 2008). The chromosome 22q11.2 deletion syndrome is typically associated with a variety of complex medical (e.g., cleft palate, congenital heart defects, facial anomalies, immune function, velopharyngeal dysfunction), developmental (e.g., speech difficulties, learning/developmental disorders, poor motor/balance and coordination, social deficits), and psychiatric issues (e.g., psychosis, anxiety, ASD, attention-deficit/hyperactivity disorder; Goldenberg et al., 2012; Gothelf, 2014; Stoddard et al., 2010; Tang et al., 2014). Individuals with 22q not only demonstrate a genetic vulnerability for psychiatric disorders, but are also more likely to endorse the presence of a variety of stressors. Additionally, these individuals are more likely to experience repeated or chronic stress than their typically developing counterparts. One such form of chronic stress is bullying. Although currently limited, emerging research on bullying among youth with disabilities report that they are 1.5 times more likely to be victimized (Blake et al., 2012) and become involved in bullying through various roles (McLaughlin et al., 2010; Rose et al., 2015; Rose et al., 2011).

Exposure to chronic stress, like bullying, in conjunction with increased genetic risk may have a significant impact on the development of psychosis in this population. To date, there has not been an in-depth investigation into the effect of bullying in individuals with 22q in general, let alone the possible relationship this form of chronic stress has on risk for psychosis specifically. We propose that bullying may have an even greater impact on individuals with 22q11.2 deletion syndrome due to the increased risk associated with multiple physical, developmental, intellectual, and psychiatric vulnerabilities. In this review, we first present 1) an overview of the impact of stress on psychological and functional outcomes in 22q, 2) the impact of bullying for individuals with and without special needs, and 3) the potential role of bullying as a chronic stressor leading to expression of psychosis risk in 22q.

## 2. 22Q11.2 Deletion syndrome

As previously stated, individuals with 22q show higher rates of psychiatric comorbidities particularly for anxiety disorders (36%), ADHD (37%) and psychosis spectrum disorders (10% in adolescents, 41% in adults) according to a recent study conducted by Schneider et al. (2014). Additionally, a study by Yi et al. (2014) illustrated that those with 22q and congenital heart disease (CHD) had greater risk for developing psychosis spectrum disorders with 71% of the sample meeting criteria. Most individuals with 22q have borderline to low average IQ scores, and they typically perform better in verbal than non-verbal tasks (De Smedt et al., 2007; Woodin et al., 2001). Individuals with 22q have significant global and domain specific cognitive impairments which have been shown to correlate with not only role but social functioning (Campbell et al., 2015).

Despite the increased risk factors for bullying in this population, there are currently no known studies that have specifically examined bullying perpetration or victimization among individuals with 22q. As a relevant comparison, children with chronic illness, complex medical conditions (e.g., asthma, inflammatory bowel disease, diabetes), and motor skills/coordination difficulties all have been noted to be at increased risk for bullying victimization (Bejerot et al., 2013; Faith et al., 2015; Pittet et al., 2010). Given the host of medical, physical, and neurodevelopmental challenges that typically present in individuals with 22q, there is a real concern about their increased risk factors for bullying victimization.

## 3. Impact of stress on individuals with 22Q

### 3.1. Prevalence of anxiety disorders

Research on individuals with 22q suggests that stress and anxiety levels are important considerations in the development of psychosis. In general, early Adverse Childhood Experiences (ACEs) increase the risk of developing later anxiety disorders and are associated with atypical development of physiological stress responses (Elzinga et al., 2008). Youth with 22q commonly experience anxiety disorders such as specific phobia, separation anxiety, and generalized anxiety disorder ranging from 32% to 61% (Dekker and Koot, 2003; Gothelf et al., 2007). Additionally, due to the medical comorbidities of the deletion (e.g. cleft palate, heart abnormalities), youth with 22q also experience a number of medical procedures and surgeries early in their life, which can increase the risk of anxiety disorders due to the stress of medical trauma experienced (Beaton and Simon, 2010). Higher anxiety scores among youth with 22q have also been associated with lower adaptive functioning (Angkustsiri et al., 2012). A significant negative correlation is noted among youth with 22q who endorse symptoms associated with fear of parental separation and fear of physical injury with their adaptive functioning (Angkustsiri et al., 2012). Individuals with 22q who go on to develop schizophrenia were more likely to have accompanying symptoms of anxiety and lower verbal IQ scores over time (Goldenberg et al., 2012). Given the complex nature of the role that stress and anxiety plays on the psychopathology of youth with 22q, additional research is warranted to determine how elevated levels of stress and comorbid anxiety disorders contribute to the emergence of psychosis symptoms in this population.

### 3.2. Social cognition and functioning

Furthermore, social cognition deficits have been identified in the development of psychosis in 22q. Specifically, in youth with 22q, theory of mind is a significant predictor in the development of positive symptoms, while processing speed is a significant predictor of negative symptoms (Jalbrzikowski et al., 2012). Similar to individuals with schizophrenia without 22q, social cognition impairments (e.g., emotional processing, theory of mind) have also been reported, along with some difficulty among their first-degree relatives (Jalbrzikowski et al., 2012).

Social relationships have been suggested as an important buffer against traumatic experiences (Yang and McLoyd, 2015). Beaton and Simon (2010) highlighted that the role of parents' coping ability and level of socio-emotional support may contribute as a risk or protective factor psychosis risk for youth with 22q. Due to their early medical, developmental, and learning difficulties, youth with 22q come to rely on their parents for most of their daily needs and may continue to do so for a longer duration of time compared to their same-aged peers, depending on their adaptive functioning abilities and independent living skills. Thus, it would make sense that when bullying is an issue for youth with 22q, their parents' coping abilities, modelled ways of dealing with everyday stressors associated with interpersonal conflicts, and level of social support would contribute to some extent in youth's level of chronic stress, thereby impacting their risk or protection from developing psychosis (Beaton and Simon, 2010).

## 4. Bullying involvement and related outcomes

Bullying is an act of repeated aggression or intimidation towards another where an imbalance in power exists between individuals (Arseneault et al., 2010; Olweus, 1993; Vaillancourt et al., 2009). It is also a form of adverse childhood experience (ACE (Radford et al., 2013); which usually involves some form of physical violence, intimidation, ridicule, name-calling, social exclusion, and/or extortion. Early research on the nature of bullying considered it a common psychosocial problem during school age years, and the general public viewed bullying as a typical childhood experience that is typically resolved (Arseneault et al., 2010).

Early adolescence (ages 12–14) marks the highest prevalence rates of bullying victimization at 25–27% (Lessne and Yanez, 2016; Whitney et al., 1992). Recent national data suggests that 20% of school aged youth are the victims of bullying during an academic year (Lessne and Yanez, 2016). Researchers have identified groups that are specifically vulnerable to bullying, such as lesbian, gay and other sexual minority individuals, youth with weight problems, and those with learning/developmental disabilities.

As previously stated, bullying is a form of adverse childhood experience (ACE), and the number and chronic nature of ACES experienced by an individual is associated with health outcomes. There are three roles involved in a given bullying situation: 1) the pure "bully" (i.e., perpetrates, but no victimization); 2) the "bully/victim" (i.e., has been a bully and a victim); and 3) the pure "victim" (i.e., has never been a bully; Berger, 2007; Wolke et al., 2014). Olweus (2001) introduced a more nuanced definition of the various roles involved in

a bullying situation (e.g., students who bully, followers, passive bullies); we refer readers to this work for additional information.

Bullying victimization occurs in 1 out of 5 school-aged youth (Lessne and Yanez, 2016). Prevalence of bullying victimization is comparable across the biological sexes (Centers for Disease Control and Prevention, 2014; Finkelhor et al., 2015). In contrast, males are more likely to be bullying perpetrators and bully/victims than females (Cook et al., 2009). Due to the overt nature of physical bullying, adults (i.e., school staff, parents) tend to be more aware of its occurrence when it involves males than females (Undheim and Sund, 2010). Somewhat higher rates of victimization occur among Caucasians (21.6%) and African-Americans (24.7) (Lessne and Yanez, 2016).

Victimization is more common for youth with low self-esteem and who are socially isolated, have poor interpersonal skills, and those who are perceived as “different” or “easy targets” (Arseneault et al., 2010; Centers for Disease Control and Prevention, 2016). Risk factors for bullying victimization are based on both environmental factors (e.g., low socioeconomic status, school overcrowding, and child maltreatment in the home) (Arseneault et al., 2010; Barnes et al., 2006; Shields and Cicchetti, 2001; Wolke et al., 2014) and genetic factors (e.g., temperament, aggression, internalizing problems, externalizing problems, existing medical/neurodevelopmental vulnerabilities) (Arseneault et al., 2010; Schreier et al., 2009; Shakoor et al., 2015). Several studies indicated that heritable traits accounted for approximately 35% of the increased propensity for bullying victimization (Arseneault et al., 2010; Schreier et al., 2009; Shakoor et al., 2015). This presumes that there is no single cause for bullying, and that various individual, familial, and environmental factors are at play (Olweus et al., 1999).

Studies show that any involvement in bullying (i.e., as a pure bully, bully/victim, or pure victim) is associated with poorer psychological functioning (Kelleher et al., 2008; Wolke et al., 2014) in both childhood and adulthood. In childhood, bullying perpetration is linked to higher rates of maladjustment, substance use, truancy, vandalism, aggressive behaviors (e.g., carrying weapons), school dropout, psychosomatic problems, and increased risk for psychosis at age 18 (Gini, 2008; Nansel et al., 2001; Olweus, 1993; Solberg and Olweus, 2003; Wolke et al., 2014). Victims of bullying are more likely to develop depressive and anxiety symptoms, sleep problems, and experience poor academic functioning (Centers for Disease Control and Prevention, 2016). Additionally, the experience of being a bully/victim results in an even greater risk of developing externalizing symptoms (aggression, conduct problems), internalizing symptoms (depression, suicidality), negative sense of self and others, poor social skills, peer rejection, severe psychopathology, physical health concerns, and higher adjustment problems than pure victims (Arseneault et al., 2010; Arseneault et al., 2006; Holt et al., 2015; Hunter et al., 2014; National Academies of Sciences, 2016). In adulthood, bullying history has been associated with a variety of poor long-term outcomes, with serious mental illness and psychosis being the most significant (Ashford et al., 2012; Bentall et al., 2012; M. L. Campbell and Morrison, 2007; De Loore et al., 2007; Kelleher et al., 2008; Kelleher et al., 2013; Lataster et al., 2006; Tunnard et al., 2014).

### 4.1. Bullying risks and outcomes related to youth with special needs

ACEs pose added negative implications to the general course of childhood development, and it may be more detrimental to youth with concurrent disability status, medical issues, and/or neurodevelopmental disorders. A substantial number of studies have confirmed that the rate of bullying victimization is higher among youth with special needs (60%) in comparison to typically developing (TD) children (10–27%; (Estell et al., 2009; Nansel et al., 2004; Thompson et al., 1994; Whitney et al., 1992). Individuals with disabilities are twice as likely to be involved in bullying victimization (Rose and Monda-Amaya, 2011; Whitney et al., 1992) in comparison to TD youth (Whitney et al., 1992).

Despite their disability status, studies indicate that youth with special needs also participate as bully/victims and bullying perpetrators (Maïano et al., 2016; Rose et al., 2015; Rose and Monda-Amaya, 2011). A study by Maïano et al. (2016) showed that bullying experiences in youth with special needs includes participation as victims (36.3%), bully/victims (25.2%), and bullies (15.1%). Interestingly, the prevalence rates obtained for bullying perpetration among youth with intellectual disabilities (ID) were similar to those from studies on TD youth (Due and Holstein, 2008; Nansel et al., 2004). A study by Schrooten et al. (2016) showed that adolescents with autism spectrum disorders (ASD) endorsed higher bullying perpetration towards others(6.2%) than TD (3.9%) despite having greater social impairment. Bullying perpetration by youth with special needs may be due to previously learned behaviours from school-aged peers, or as a way to address past victimization (Schrooten et al., 2016; Whitney et al., 1992).

Further variability in the bullying and victimization prevalence rates among different subgroups of youth with special needs have been indicated (Rose and Monda-Amaya, 2011; Van Roekel, Scholte and Didden, 2010). For youth with moderate to mild intellectual disability (ID), the risk for bullying victimization is higher compared to children in mainstream classrooms (Thompson et al., 1994). In general, low social support (i.e., few peer friendships) was identified as a risk factor for bullying among youth with special needs (Thompson et al., 1994). As such, there is an evident need to protect the vulnerable youth with special needs from avoidable harm.

## 5. The interplay of bullying and vulnerability in psychosis symptom development for 22Q

Genetic risk for the development of psychosis has been well documented in individuals with 22q. Studies have shown similar genetic and enzymatic disruptions in individuals with 22q and those with schizophrenia. Specifically, studies have shown disruption in Catechol-O-methyltransferase (COMT) which is a gene that encodes a key dopa-mine catabolic enzyme. This gene has been implicated in genetic models of schizophrenia and is notably located in the area of deletion associated with 22q11 deletion syndrome. Similarly, proline dehydrogenase (PRODH) is gene that is involved in glutamate production and has been shown to be both affected by the microdeletions associated with 22q and correlated with development of juvenile onset schizophrenia. A comprehensive review of the genetic risk

and vulnerability for the development of psychosis in individuals with 22q can be found here (Williams and Owen, 2004).

Individuals with 22q are uniquely vulnerable to experience both bullying and the development of psychosis spectrum disorders. Several studies on youth with 22q have attributed it to the compounding effects of chronic stress, anxiety, and trauma on poor adaptive functioning and increased risk for psychopathology (Angkustsiri et al., 2012; Beaton and Simon, 2010; Gothelf et al., 2007; Schneider et al., 2014). Beaton and Simon (2010) proposed that a cascade of chronic elevated stress, negative life events, and poor coping skills among youth with 22q place them at elevated risk for psychosis.

A recent review on the relationship between trauma and psychosis risk among CHR individuals suggests an initial genetic vulnerability that interacts with traumatic experiences (Mayo et al., 2017). The interplay between genetics and early traumatic events places individuals at an altered developmental trajectory and at greater risk for psychotic-like experiences. With the emergence of subthreshold symptoms of psychosis, one is exposed to increased risk for future instances of trauma. This proposed trauma-psychosis relationship offers a promising way of further understanding the relationship between bullying and psychosis risk among individuals with 22q. Additional research is needed to investigate the interaction between the 22q population's traumatic experiences (specifically bullying) and elevated psychosis risk (see Fig. 1). As can be seen in Fig. 1 the interplay between stress and genetic vulnerability is cyclical. An initial stress-related insult on genetically vulnerable individuals can lead to attenuated psychosis symptoms. Continued stress then exacerbates existing symptoms, possibly contributing to threshold psychotic experiences. We will discuss these dynamic interactions below.

### 5.1. Early and chronic stress

In infancy and toddlerhood, many children with 22q are affected by multiple medical and immune system complications, which often lead to early invasive, complex surgeries, and possibly repeated medical interventions. Individuals with 22q become increasingly aware of their individual differences in academics and social abilities from TD peers in the school setting. Social adjustment to their same-aged classmates may be more challenging and associated with increased shyness, withdrawal from others, and poorer self-image or self-esteem due to difficulties in speech and differences in physical appearance or abilities. In addition, youth with 22q who have ID and poorer adaptive functioning abilities may be prone to increased risk for bullying and victimization. As explained by Angkustsiri et al. (2014), it may be expected that, with continued exposure to negative social interactions, youth with 22q would experience increased anxiety in emotional difficulties due to poor social competence. Consequently, such repeated and chronic stressors during critical developmental periods can lead to the dysregulation of their hypothalamic-pituitary-adrenal (HPA) axis (Lupien et al., 2005; McEwen, 2014). The early negative experience of bullying victimization may promote HPA axis dysregulation and possible exhaustion of coping resources. Indeed, a dose-response relationship has been indicated regarding the number of victimization events in early childhood and the increased risk for psychosis symptoms in early adolescence (Arseneault et al., 2010; Bentall et al., 2012; Kelleher et al., 2013;

Schreier et al., 2009). Over time, it is possible that prolonged HPA axis dysregulation due to bullying experiences may lead to increased high risk for psychosis among individuals with 22q.

Individuals with 22q deletion syndrome are one example of a special needs population that report high rates of ID, medical, and neurodevelopmental impairments that may be at increased risk for bullying involvement. Specifically, most individuals with 22q struggle with social and interpersonal situations due to poor social cognition (e.g., theory of mind, interpretation of social cues), emotional recognition, processing speed, and verbal reasoning (Goldenberg et al., 2012; Jalbrzikowski et al., 2012). While individuals with 22q have been described to have age-expected levels of social interest and motivation, they are generally far less socially competent then their same-aged peers; instead, some are more successful at making and maintaining friendships with developmentally-matched peers who are chronologically younger (Angkustsiri et al., 2014; Norkett et al., 2017). Due to co-occurring genetically-mediated developmental, physical, and learning difficulties, youth with 22q are more likely to negatively stand out among their peers (Angkustsiri et al., 2012; Jalbrzikowski et al., 2015; Jonas et al., 2014; Niarchou, Martin, Thapar, Owen, & van den Bree, 2015; Tunnard et al., 2014). The occurrence of borderline cognitive abilities and poor interpretation of social situations may result in poor social competence and elevated risk for being a target of bullying victimization (Angkustsiri et al., 2014; L. E. Campbell et al., 2015).

### 5.2. Bullying and psychosis risk

Longstanding bullying victimization has been associated with negative psychological development and may contribute to the development of serious mental illness such as psychosis. A history of bullying victimization has been linked to an increase in psychosis symptoms, particularly symptoms of suspiciousness or paranoia in individuals with established psychotic illnesses (Shakoor et al., 2015; Trotta et al., 2013; Valmaggia et al., 2015). Additionally, studies indicate that increased severity and duration of bullying victimization were significantly associated with the emergence of psychosis symptoms in clinical high-risk (CHR) individuals (Addington et al., 2013; Bebbington et al., 2004; Schreier et al., 2009; Van Dam et al., 2012). An examination of individual symptoms demonstrated a trend with regards to clinical suspicion, showing elevated endorsements symptoms of suspiciousness in individuals with a reported history of bullying victimization in both CHR and TD individuals (Valmaggia et al., 2015). Researchers have hypothesized that this increase in symptoms in TD, CHR, and clinical symptomatic populations may be attributed to maladaptive behaviours and negative coping styles learned during the sensitive period of adolescent development. Indeed, a study found that internalizing problems mediated the relationship between bullying victimization and psychosis symptoms (Fisher et al., 2013). Individuals who reported having negative attributional styles and endorsed a history of bullying victimization were more likely to find supporting evidence for their hostile and threatening views of the world (Shakoor et al., 2015). Additionally, early psychotic experiences may mediate the relationship between bullying and adulthood psychosis symptoms (Wolke et al., 2014). Though not all individuals who experience trauma are expected to develop such psychotic-like experiences, however, an individual's risk

increases as a result of their environmental, as well as genetic, factors. Overall, while most of the current research suggests that bullying victimization is associated with increased risk for developing psychosis symptoms during adolescence and later adulthood (Shakoor et al., 2015; Trotta et al., 2013), some studies have failed to confirm this relationship (Bentall et al., 2012). However, it is important to note that the impact of bullying does not simply attenuate over time, and that it can have negative long-term effects on mental health status.

## 6. Conclusion

Stress and anxiety are known factors that contribute to onset of serious mental illness and have been linked to the development of psychosis in 22q (Beaton and Simon, 2010). Due to the genetic vulnerability for psychosis and its potential interaction with stress that exists in the 22q population, it is essential to further explore the impact of both bullying perpetration and victimization among youth with 22q and its potential role in the development of psychosis symptoms. Due to the high risk for psychosis in youth with 22q, the careful and ongoing assessment of daily stress and anxiety is important. While not everyone with 22q and or who has experienced bullying is expected to develop any lifetime symptoms of psychosis, it is important to carefully monitor when bullying occurs due to the cascade of negative physical and mental health outcomes that goes along with bullying perpetration and victimization.

## Acknowledgements

Funding for the current study was supported by the NIH Grant Project #3R01MH107108.

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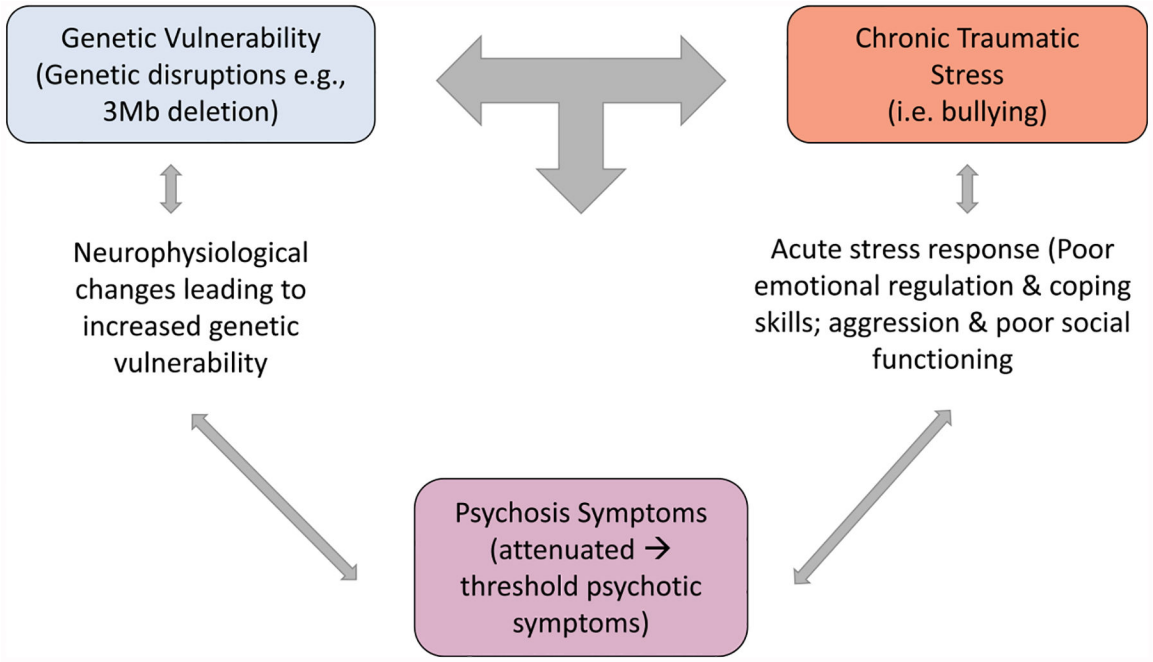


**Fig. 1.**
Interaction between genetic risk, chronic stress, and psychosis.