Psychiatric implications of stress for children with 22q11.2 deletion syndrome

Elliott A. Beaton, Ph.D.
University of California, Davis Medical Center, M.I.N.D. Institute, Sacramento, CA, USA
Cognitive Analysis and Brain Imaging Lab
http://cabil.mindinstitute.org/
Contact email: eabeaton@ucdavis.edu

Outline

• Understanding stress, anxiety, and mood
• Why study stress and anxiety in this children with 22q11.2DS?
• Description of ongoing studies of developmental indicators and/or markers of risk
• Implications and Future Work

What do we mean when we talk about “stress”, “anxiety”, and “depression”?

Stress has been defined many ways…

• Stress = any shift from homeostasis (Cannon, 1932)

• The psychophysiologival consequence of any event challenging the organisms capacity to cope (Selye, 1946)

• Stress can also be thought of as a motivational state that arises from emotional/cognitive processes and bodily states

Stress and Anxiety

• Are related and can share symptoms but not exactly the same

• Anxiety can be specific or generalized

• Doesn’t always disappear with a reduction in obvious stressors

• Anxiety can elicit a strong physiological stress response.

What about depression?

• Anxiety and depression are not the same thing but they can share some similar symptoms (e.g. irritability, problems sleeping or concentrating, HPA dysregulation)

• It is not uncommon for people with a mood disorder to be diagnosed with an anxiety disorder (and vice versa)

• Chronic stressors that seem uncontrollable and unchangeable combined with self-blame for a situation or your inability to deal with it may lead to depression (Seligman, 1992)
What’s ‘allostatic (over) load’?

- Allostasis = actively maintaining homeostasis through change (Sterling & Eyer, 1988; McEwan, 2000)
- Allostatic load is the “wear and tear” on the body with repeated/chronic effort to maintain allostasis
- Think of it as getting a loan to get through hard times that you plan on paying back…

Why study this?

- Understanding the effects of mood, anxiety, and stress in kids with 22q11.2DS has clear short-term benefits and may have important long-term benefits
- Early intervention could improve quality of life now and may protect against mental illness in adolescence/young adulthood

Anxiety can affect (and arise from) impairments in adaptive skills

Schizophrenia in 22q11.2DS

- Approximately 25-30% of children with 22q11.2DS will develop schizophrenia or psychotic depression in young adulthood.
- In an unselected population of patients with a schizophrenia Dx, 2% will have the 22q11.2 deletion (Basset et al., 2003)

22q11.2DS = variable presentation

- Low phenotypic-genotypic correlation
- Symptoms in monozygotic twins may vary significantly
- Mediating copy number variants, gene-gene interaction outside deletion zone and environmental factors have not yet been clearly elucidated.
- The deletion is neither necessary nor sufficient for schizophrenia…

Why is the risk so much higher for kids with 22q11.2DS?

(Hillebrand et al., 2000; Matsuoka et al., 1998; Yamagishi et al., 1998; Singh et al., 2002; Goodship et al., 2000)
How do we predict who will develop schizophrenia?

• This is a very significant concern for parents
  – There are more resources and support for children and less for adolescents and adults
  – There may be key windows-of-opportunity where interventions are most effective

Stress and Schizophrenia

– The stress-diathesis model of schizophrenia (e.g. Walker, 2008)
  – Think of a pin hole in a rubber band…where would it break?
  – Applies to ‘typically-developing’ people without known genetic deletions so, why not 22q11.2DS?

Our argument…

– Some risk may be explained by the physiological and psychological effects of chronic and/repeated stress.

WARNING: STRESS DOES NOT CAUSE SCHIZOPHRENIA

A person’s ability to cope with stress is driven by an interaction amongst genetically derived temperament, experiences, and environment.

Kids and families with 22q11.2DS can have a lot to cope with!

– Early major medical interventions and infections
– Socioemotional impairments
– Cognitive impairments that complicate education (math, time, etc.)
– Co-morbid for other Dx (ADHD, OCD)
– Problems become more prominent with increasing social and academic demands.

Early traumatic experiences can also affect that way a person copes with stress later in life.
Changes in coping styles may be behavioral and not always positive.

“Patient A”
- Background: 11y11m, ♀, entering 6th grade (repeated 3rd), (associated with ADHD-inattentive type dx)
- Behaviors
  - School: Inattentive, oppositional, defiant. During 5th grade she closed herself in a locker and enclosed herself in gym-bag. Assigned to ½-days. Difficulty advocating with school due to her adequate achievement.
  - Home: Inattentive, oppositional, defiant. Her main recreational activities involve using her blackberry or handheld computer games. She took intimate, cell-phone photos of herself in order to become “popular.”
  - Clinic: Oppositional, tearful, defiant, “glaringly angry” at her mother. Ariane was easily flooded by task demands, low frustration tolerance.

Temperament and susceptibility to stress may be regulated in part by genes in the deleted region.

Catechol-O-methyl transferase (COMT)
- Gene is located in the 22q11.2 deleted region
- Hemizygous in individuals with 22q11.2DS
- Enzyme that degrades catecholamines (dopamine, norepinephrine)
  - High activity allele: Val
  - Low activity allele: Met
  - met/met individuals have 4-fold reduction in activity level compared to val/val

COMT and Psychosis in 22q11.2DS
- Was studied in the context of the DA hypothesis of schizophrenia but no clear relationship.
- Time 1 anxiety and mood, lower verbal IQ, with low activity catechol-O-methyltransferase (COMT) genotype predicted onset and severity of psychosis in 22q11.2DS at T2 (Gothelf et al., 2007).

What else does COMT do?
- Low activity COMT variant is associated with:
  - greater stress sensitivity (Van Winkel et al., 2008)
  - Greater PFC, amygdalar, hippocampal activation to negative faces (Simonska et al., 2006; Drabant et al., 2008)
- Interacts with polymorphic variants of genes that code for monoamine oxidase A and serotonin transporter
  - affecting ACTH and HPA reactivity/feedback
  - Increased risk of depression and anxiety (Jabbi et al., 2007)
So, COMT activity may also contribute to stress susceptibility in conjunction with other factors that include other genes and life experiences.

Think of each of these factors are like the tumblers in a lock...

Chronic stress has physiological effects on the body that are helpful in the short term but can be damaging if prolonged.

The (limbic) hypothalamic-pituitary-adrenal (HPA) axis is part of your body’s stress-response system.

Why measure cortisol?

• Cortisol is a metabolic and “stress” hormone

• Chronic and especially unpredictable stressors = prolonged HPA-axis activation = persistent elevated cortisol release

Effects of chronic cort on development of at-risk kids?

• Chronic elevated glucocorticoid secretion:
  – seen w/ depression and anxiety
  – Immunological impairments
  – Neuronal death, greater vulnerability to neurotoxicity, reduced neurogenesis, and decreased dendritic arborization in the hippocampus (McEwen 1999; Sapolsky et al., 1985; 1986).
Mean CDI total and subscale T-scores for the whole sample (a) and those children with cortisol measures (b).

Mean MASC total and subscale T-scores for the whole sample (a) and those children with cortisol measures (b).

• Passive drool saliva collection
• Pre and post mock scanner training procedure
• Novel experience + mild ‘restraint’ stress should elicit a mild stress response
• Stress should dissipate quickly as the child acclimates to the environment

Total and Post-practice salivary cortisol was higher in children with 22q11.2DS vs. TD

Salivary cortisol over 2 school days and one home day in children with and without 22q11.2DS

Developmental effects of stress and origins of stress sensitivity may be reflected in the morphology of the brain.
Kates et al., 2006

- Children with 22q11.2DS vs. sibs and non-sib controls
  - In 22q11.2DS, larger amygdala volumes and smaller hippocampus
  - Larger amygdala volumes w/ smaller amygdala/PFC ratio = more anxiety, internalizing, externalizing and aggression on CBCL
  - Suggestive of prefrontal-amygdalar circuit disruption = emotion dysregulation?

- Chronic elevated GC may have deleterious effects on hippocampal and amygdalar development.
  - Children and adults with 22q11.2DS show characteristic decreases in hippocampal volume (Debbané et al., 2006; DeBoer et al., 2007).
  - Abnormal development of these neural structures can in turn increase stress sensitivity, dysregulation of the HPA-mediated stress response, with deleterious effects on verbal, working, and spatial memory.

Structural Correlates of Stress and emotional dysregulation

![Coronal and Sagittal Slices](Adapted with permission from Schumann, Amaral, et al. 2004)

Hippocampal volumes for children with 22q11.2DS and TD children

![Hippocampal Volume Graph](Beaton et al., ongoing study)

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Recap of our argument...

- 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.
Implications of this work

- This is an ongoing prospective study.
- We can treat anxiety and teach coping skills.
- Interventions could be tailored to potentially “bump” developmental trajectories in a positive direction.
- We may learn what factors are protective against stress and anxiety (and potentially schizophrenia) from children with 22q11.2DS as well.

Science, Policy, and Parents

NIMH Area of High Priority

- Division of Developmental Translational Research
  - “Delineate neurobehavioral mechanisms responsible for the development of psychopathology, including critical and sensitive periods in brain development and the effects of sex, behavior, and experience on the brain.”
  - “Develop, test, and validate biologically based markers (e.g., genetic, proteomic, imaging) to improve diagnosis, identify risk indicators in order to preempt disorder, serve as criteria to personalize treatment, and evaluate treatment response.”

The at-home saliva study is ongoing…

…and we need your help to continue this important work.

- Please contact Elliott Beaton to participate.
  Phone: 916-703-0408
  Email: eabeaton@ucdavis.edu
Thank you.

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