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Review

Severe stress and the development of the amygdala in youth: A theory and its statistical implications

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ABSTRACT

An empirical understanding of normal developmental variation in the amygdala is emerging. However, studies examining volumetric differences in the amygdala among patient populations, particularly individuals with posttraumatic stress disorder (PTSD), have not produced a consistent pattern of findings. One reason for this may be the failure to effectively address age variation in study design and data analysis. Findings on age related variation in human amygdala volumes as well as the role of stress on amygdala development are reviewed. A theory is developed which posits that normal developmental variation in amygdala volumes may be altered under conditions of severe stress. Specifically, that stress may delay, accelerate, or prolong typical growth patterns. The theory highlights identifying the factors related to either delayed, accelerated, or a prolonged period of growth. The theory also points to systematically testing age as an interactive (moderator) variable in pediatric and psychiatric neuroimaging research. This is because the theory implies that disorder status/exposure to severe stress may influence the relationship between age and amygdala volumes.

Introduction

The amygdala is a brain region of the anterior portion of the temporal lobes. Its main functions are thought to be involved in the evaluation of the emotional significance of incoming stimuli (Tottenham, 2012; Tottenham & Sheridan, 2010). The amygdala projects to several brain structures in the frontal cortex, the hippocampus, the striatum, the hypothalamus, and brain stem (see Gordon & Hen, 2004; LeDoux, 2000; Tottenham, 2012; Tottenham & Sheridan, 2010). Because of its structural connections and functionally identified roles, the amygdala is considered to have critical involvement in behavioral activation (approach) and inhibition (withdrawal) systems underlying emotional responses such as fear and anxiety and their regulation (Gray, 1994; Gray & McNaughton, 2000). Activation of the behavioral inhibition system is associated with fear, anxiety, and negative emotionality. Because of this link, the amygdala has received particular attention in biological theories of anxiety and stress related disorders such as posttraumatic stress disorder (PTSD) as well as other disorders involving emotion dysregulation (e.g., Davis, 1998; LeDoux, 2000).

Understanding the development of the amygdala has implications for emotional health and emotional disorder research given its role in the evaluation of the emotional significance of stimuli. While the empirical data is emerging, several factors may shape brain development in youth. Identifying developmental influences, such as parenting and stress, which may be

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associated with differential brain development is an important task (Belsky & de Haan, 2011). A number of perspectives suggest there may be differences in amygdala volumes among individuals exposed to severe or traumatic stress (Karl et al., 2006; Morey et al., 2012; Tottenham & Sheridan, 2010; Tottenham et al., 2010; Woon & Hedges, 2008, 2009). However, studies examining volumetric differences in the amygdala among individuals with PTSD have not produced a consistent pattern of findings. For example, Morey et al. (2012) reviewed 12 studies on amygdala volumes among individuals (9 adult samples and 3 youth samples) with posttraumatic stress and reported four studies indicating relatively smaller volumes (in both sides); one relatively smaller in the left, but larger in the right; one study relatively smaller in the right, larger in left; and six relatively larger in both sides (compared to control participants). Only 1 of these 12 reported p-values reached the typical 0.05 alpha to indicate a statistically significant difference and so one conclusion might be that there is a consistent picture of non-statistically significant differences.

In this paper, findings on age related variation in human amygdala volumes as well as the role of stress on amygdala development are reviewed. A theory is developed which posits that normal developmental variation in amygdala volumes may be altered under conditions of severe stress. Specifically, that stress may delay, accelerate, or prolong normal growth. The theory highlights identifying the factors related to either delayed, accelerated, or a prolonged period of growth. The theory also points to systematically testing age (and other indices of maturation like pubertal development) as an interactive variable in pediatric and psychiatric neuroimaging research.

Normal developmental variation

There is fairly clear evidence that the amygdala develops (neuronal connections and structurally grows in size) until late childhood. Table 1 summarizes fourteen studies found in a literature search (using Medline, PsycINFO, Google Scholar, & review of references in previous publications) that have examined normal developmental variation in amygdala volumes or otherwise correlated age with amygdala volumes in various patient and control samples. Thirteen of these fourteen studies reported a statistically significant association with age (or longitudinal growth) in a community or control sample. For example, Mosconi et al. (2009) examined longitudinal change with children assessed at age two years and again at age four years and results showed that volumes increased in each group (autism and control groups). However, the findings on amygdala development suggest a complex picture. Weems, Scott, Russell, Reiss, and Carrión (2013) reported a longitudinal increase in right amygdala volumes for those in Tanner stage 1 and 2 but a decrease for those in Tanner stages 3 and 4. Moreover, in the first study suggesting continued maturation of the structure until adolescence, the amygdala was observed to be related to age in youth 4–18 years old but only for male subjects and only in the left side (Giedd et al., 1996). Laterality, of the association is also delineated in Table 1 for those studies that parceled analyses into right and left hemispheres.

Uematsu et al. (2012) examined the association of age with amygdala volumes among 109 participants (not from a clinical group but community recruited) aged from infancy to 25 years and found that a curvilinear association best defined the relationship between age and amygdala volumes (similar results in Goddings et al., 2014; Østby et al., 2009, see Table 1). The nature of the association in Uematsu et al. (2012) has potentially critical implications for research on samples with severe stress exposure. The authors report a strong linear association from infancy to around age 11 years that leveled off or declined at that point (implying no correlation or a weak negative correlation from around 10 or 11 and beyond). This curvilinear trend was observed in both the right and left amygdala. The peak growth (end of a linear association in the scatterplots) was earlier in the left side generally and earlier in females (9 years old left side – 11 years old right side) than in males (11 years old left side – 12 years old right side). The findings are consistent with a number of growth patterns where there is initially a great deal of growth that levels off (see also Goddings et al., 2014; Østby et al., 2009 with results of the leveling off occurring slightly later in development). Theoretically, this maturational variation in the amygdala may be altered by exposure to early life stress (Tottenham, 2012; Tottenham & Sheridan, 2010).

The role of stress on amygdala development

Tottenham and Sheridan (2010) have argued that adverse experiences can produce long-term changes in the amygdala structurally. In their view there is a stress-induced kindling of the amygdala where repeated stimulation produces greater future excitability and this implies potential differences in morphology. For example, among children adopted from orphanage care, Tottenham et al. (2010) reported a significant linear association between amygdala volumes and the amount of time spent in the institution when controlling for current age (the amygdala volume correlation with age was not reported). In the full sample, amygdala volumes did not differ between institutionalized children and matched comparison children, but larger volumes were found among those who spent greater than 15 months in institutionalized care (Tottenham et al., 2010). The recent theory implicating maturational differences due to institutionalized care stress (Tottenham, 2012; Tottenham & Sheridan, 2010) suggests there may be differences in amygdala volumes in youth exposed to traumatic stress.

Post-traumatic stress and the amygdala

The extant research has tended to define traumatic stress and PTSD using criteria from the Diagnostic and Statistical Manual of Mental Disorders (currently in its 5th edition; DSM-5; American Psychiatric Association, 2013), which specifies symp-

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