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Review

Emotional learning, stress, and development: An ever-changing landscape shaped by early-life experience

Siobhan S. Pattwell [a,*], Kevin G. Bath [b]

[a] Department of Human Biology, Fred Hutchinson Cancer Research Center, 1100 Fairview Ave N, Seattle, WA 98109, United States
[b] Department of Cognitive, Linguistic, and Psychological Sciences, Brown University, Providence, RI 02912, United States

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ABSTRACT

The capacity to learn to associate cues with negative outcomes is a highly adaptive process that appears to be conserved across species. However, when the cue is no longer a valid predictor of danger, but the emotional response persists, this can result in maladaptive behaviors, and in humans contribute to debilitating emotional disorders. Over the past several decades, work in neuroscience, psychiatry, psychology, and biology have uncovered key processes underlying, and structures governing, emotional responding and learning, as well as identified disruptions in the structural and functional integrity of these brain regions in models of pathology. In this review, we highlight some of this elegant body of work as well as incorporate emerging findings from the field of developmental neurobiology to emphasize how development contributes to changes in the ability to learn and express emotional responses, and how early experiences, such as stress, shape the development and functioning of these circuits.

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1. Introduction

The study of emotional memory has garnered significant interest in recent years for its inherent role in various psychiatric disorders (LeDoux, 2000). Dysregulation of emotional memory systems is a principle component in many affective disorders, including depression, specific phobias, generalized anxiety disorder, agoraphobia, and post-traumatic stress disorder (PTSD). Specifically, alterations in memory processing for aversive or traumatic experiences lie at the heart of many clinical psychiatric disorders. By studying the neural circuitry of emotional memory, and aversive learning specifically, insight can be gained into not only how these systems function normally, but also how they may go awry in the

* Corresponding author at: Fred Hutchinson Cancer Research Center, 1100 Fairview Ave North, Holland Lab, Mailstop #C3-168, Seattle, WA 98109, United States.
E-mail address: spattwel@fredhutch.org (S.S. Pattwell).

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case of pathology. By taking into account developmental, environmental, and genetic factors, the hope is that such insights will inform basic science, enhance translation to the clinic, and ultimately lead to better treatments and preventative measures for vulnerable populations.

In archetypical circumstances, fear learning is a highly adaptive, evolutionarily conserved process that allows one to respond appropriately to cues associated with danger in order to enhance future survival. In the case of psychiatric disorders, however, fear may persist long after an environmental threat has passed. This unremitting, and often debilitating, form of fear is a core component of many anxiety and stress-related disorders, including post-traumatic stress disorder (PTSD), and often involves exaggerated and inappropriate fear responses, as well as a lack of reappraisal once a stimulus no longer holds predictive validity. It is estimated that 18.1% of Americans, or 40 million people, are living with a diagnosable anxiety disorder. In the U.S. the lifetime risk for depression is 3–5% for males and 8–10% for females, the lifetime risk for PTSD is 5% for males and 10% for females, and nearly 29% of people will develop some form of anxiety disorder (Kessler et al., 2005; Murphy, Laird, Monson, Sobol, & Leighton, 2000). Affective disorders cost the American people in excess of $42 billion a year, which is approximately one third of the total $148 billion spent on mental health (AHRQ/NIMH, 2006; Merikangas et al., 2010; Merikangas et al., 2011). Furthermore, according to the World Health Organization, the burden of disease for neuropsychiatric disorders on the country exceeds that of any other medical condition, even doubling that of cardiovascular disease (AHRQ/NIMH, 2006), and anxiety disorders pose the greatest threat to mental health worldwide (WHO, 2001).

It should also be noted that the risk for affective pathology increases in late childhood and peaks during adolescence and early adulthood, indicating that either the development or the expression of affective pathology is linked to key developmental events (Burt & Stein, 2002). While these disorders are treatable in many individuals, they carry with them high rates of comorbidity and recurrence (Burt & Stein, 2002). By understanding the neural basis of stress-associated disorders and focusing on early time points, before pathology has emerged, we open up the possibility of developing better, more effective interventions, that have the possibility of preventing the development of these devastating disorders. Adolescence, in particular, is a period associated with increased prevalence of psychopathology involving perturbation of emotion (Monk et al., 2003), and it is estimated that over seventy-five percent of adults with fear-related disorders met diagnostic criteria as children and adolescents (Kim-Cohen et al., 2003; Pollack et al., 1996). Pediatric and adolescent-onset anxiety disorders are associated with increased symptom severity compared to disorders that emerge later in adulthood. Despite the fact that diagnosis of anxiety disorders peaks in pediatric and adolescent populations (Kessler et al., 2005; Merikangas et al., 2011; Newman et al., 1996), fewer than one in five children or teens are expected to receive adequate treatment (Keller et al., 1992; Liberman, Lipp, Spence, & March, 2006; Merikangas et al., 2010). In addition to developmental aspects, genetic variants, combined with environmental exposures to physiological and psychological stressors, can profoundly impact neural substrates implicated in fear and anxiety, rendering specific populations more or less susceptible to developing psychiatric disorders at different stages of their lives.

Specifically, early life stress (ELS) significantly increases the risk for the later development of affective pathology. A single stressor experienced during childhood increases the lifetime risk of anxiety or depressive pathology by approximately 30% (Anda et al., 2006). Sixty-four percent of individuals will experience at least one significant stressor during childhood (Anda et al., 2006). Having three or more adverse experiences early in life more than doubles the lifetime risk of developing affective pathology (Anda et al., 2006). In addition, there is a significant sex disparity in the incidence of affective disorders, with females being nearly twice as likely as males to develop pathology (Breslau, 2009; Breslau, Davis, Andreski, Peterson, & Schultz, 1997; Breslau, Davis, Peterson, & Schultz, 1997; Burt & Stein, 2002; De Munck, Portzky, & Van Heeringen, 2009; Felitti et al., 1998; Gater et al., 1998; Hankin, 2009; Keita, 2007; Kuehner, 2003; Olino, Klein, Lewinsohn, Rohde, & Seeley, 2010; Weissman et al., 1996; Weissman et al., 2005).

For animals, human encroachment and climate change have led to loss of habitat (and breeding grounds) and destruction of food sources. In humans, increasing civil unrest, famine, and poverty have resulted in an unprecedented 65 million individuals being displaced and nearly 650 million children worldwide who lack adequate shelter, water, or health services. Across species, these effects have diminished the ability of parents to care for and nurture offspring, increasing the incidence of early life stress, with consequences for emotional and behavioral development that extend beyond borders and across species. The goal of this review is to provide novel insight into the development of key circuitry supporting the development of emotional learning and emotional regulation and the mechanisms by which changes in species expected environments, such as diminished early life care, alter the development of these processes.

Many forms of emotional pathology are thought to have their root in aberrant development of brain regions responsible for emotional responding as well as emotion regulation. Specifically, several key regions associated with the control of emotional learning have been identified, including the amygdala, hippocampus, and sub-regions of the prefrontal cortex. Recent work has identified unique effects of developmental status, exposure to early life stress, as well as genetic background on the development and functioning of these brain structures. Specifically, work from our lab has found that exposure to early life stress is associated with a precocious process of maturation for at least a subset of these structures, effects that are mirrored in human studies of functional brain activation to emotional cues and functional connectivity. How these changes contribute to increased risk for pathological outcomes, as well as the molecular drivers of altered maturation of these regions represent a fertile area of investigation to potentially identify the neural substrates of pathology, and to identify both novel treatments as well as optimal timing of intervention. Critical work, leveraging models of emotional learning that can be tracked over developmental time frames have the potential to shed light on this important question.

2. Modeling fear in the laboratory: Pavlovian conditioning

Considered by many to be the father of modern neuroscience, Santiago Ramon y Cajal stated over a century ago that “the brain is a world consisting of a number of unexplored continents and great stretches of unknown territory” (Farndon, 2009). While many unanswered questions about the brain undoubtedly remain, great advances in recent years have uncovered a wealth of information about the neural circuitry involved in fear acquisition, expression, and extinction, offering glimpses into anxiety disorder etiology and treatment.

Fine-grained work in nonhuman animals combined with advances in functional neuroimaging (through PET and fMRI scans) have revealed neural processes involved in fear regulation. Observations across clinical patient cases, healthy human subjects, and non-human animals all substantiate a preservation of fear acquisition and extinction learning mechanisms and basic architecture across species. As a result, rodent models have the potential to