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Endogenous opioid system influences depressive reactions to socially painful targeted rejection life events

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Summary Although exposure to a recent major life event is one of the strongest known risk factors for depression, many people who experience such stress do not become depressed. Moreover, the biological mechanisms underlying differential emotional reactions to social adversity remain largely unknown. To investigate this issue, we examined whether the endogenous opioid system, which is known to influence sensitivity to physical pain, is also implicated in differential risk for depression following socially painful targeted rejection versus non-targeted rejection life events. Adolescents ($n = 420$) enrolled in a large longitudinal birth cohort study had their recent stress exposure and current mental health status assessed using self-report and interview-based methods. Participants were also genotyped for the A118G polymorphism in the μ-opioid receptor gene (*OPRM1*, rs1799971), which has been found to influence neural and psychological responses to rejection, likely by affecting opioid receptor expression and signaling efficiency. As hypothesized, G allele carriers, who are known to exhibit less opioid receptor expression and signaling efficiency, were more severely depressed and twice as likely to meet criteria for major depressive disorder following a recent targeted rejection major life event (e.g., being broken up with, getting fired) relative to A/A homozygotes who experienced such stress. However, A118G genotype did not moderate the effects of other similarly severe major life events on depression. These data thus elucidate a biological pathway that may specifically influence sensitivity to social pain and rejection, which in turn has implications for understanding differential risk for depression and several other social stress-related disorders.

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Major life events involving interpersonal loss and social rejection are the strongest proximal risk factors for depression (Farmer and McGuffin, 2003; Slavich et al., 2010a). Stressors of this type, called *targeted rejection* life events, involve intentional social rejection and the severing of important social bonds. They thus include major life events such as being broken up with or getting fired (Slavich et al., 2009). Targeted rejection life events are associated with a 22-fold increase in risk for major depressive disorder (MDD) and precipitate MDD three times faster than other life events of comparable severity (Kendler et al., 2003; Slavich et al., 2009). These stressors have also been found to activate molecular signaling pathways that upregulate inflammation (Murphy et al., 2013), which in turn has been implicated in the pathophysiology of depression, as well as several physical health conditions that frequently co-occur with depression, including diabetes, cardiovascular disease, chronic pain, certain cancers, and neurodegeneration (Miller et al., 2009b; Slavich and Irwin, 2014). Despite these findings, many people who experience targeted rejection and other types of severe social stress do not develop depression. Moreover, the biological mechanisms underlying differential risk for MDD following these social stressors remain largely unknown. Because depression often emerges early in life and presages the development of several serious medical illnesses over the lifespan, identifying factors that shape social stress-related depression risk, especially in adolescence, is critically important (Stroud et al., 2011; Auerbach et al., 2014).

One neurobiological system that may influence risk for depression following socially painful targeted rejection life events is the endogenous opioid system. Opioids have long been known to play a central role in regulating experiences of physical pain (Basbaum and Fields, 1984; Drolet et al., 2001; Millan, 2002). Indeed, endogenous opioid neurotransmission increases during physical pain and lessens the affective experience of pain (Zubieta et al., 2001, 2002). Given the critical importance of social connection for survival, it has been proposed that neural systems originally responsible for processing experiences of physical pain may have evolved to represent experiences of ''social pain'' or rejection, perhaps to reduce the likelihood of separation from primary caregivers (Panksepp, 1998; MacDonald and Leary, 2005). Consequently, endogenous opioids may influence not only experiences of physical pain, but experiences of social pain and rejection as well (Panksepp, 2003; Way, 2013).

Several findings are consistent with this effect, which we refer to here as the *opioid rejection sensitivity hypothesis*. First, evidence has accumulated suggesting that social and physical pain are represented by similar neural systems (Eisenberger et al., 2003; Kross et al., 2011). Second, experimental studies in non-human species have shown that the μ-opioid receptor regulates behavioral distress responses to caregiver separation (Panksepp et al., 1978; Kalin et al., 1988; Barr et al., 2008). Third, positron emission tomography studies in humans have revealed that central μ-opioid signaling is altered while experiencing or recalling interpersonal loss and rejection (Zubieta et al., 2003; Hsu et al., 2013). Finally, a central analgesic has been shown to blunt neural responses to social rejection in brain systems that have been implicated in processing experiences of physical and social pain (Dewall et al., 2010). Together, these data suggest that μ-opioid signaling may modulate the experienced intensity of social rejection in addition to physical pain.

One factor that greatly alters μ-opioid signaling involves a functional single nucleotide polymorphism (SNP) in the μ-opioid receptor gene (*OPRM1*, rs1799971). Specifically, an A/G transition (A118G) within *OPRM1* leads to an amino acid change (N40D) that governs central *OPRM1* expression (Mague et al., 2009; Ray et al., 2011), leading to differences in sensitivity to both physical pain and social rejection. As evidence of these effects, patients with at least one G allele experience greater pain intensity during surgery, and require larger doses of opiates to relieve post-surgical pain, compared to A/A homozygotes (Tan et al., 2009; Sia et al., 2013). In addition, G allele carriers exhibit greater neural responses to being socially rejected, more behavioral withdrawal to angry faces indicating social rejection, and higher levels of rejection sensitivity in daily life relative to A/A homozygotes (Way et al., 2009; Bertoletti et al., 2012). Finally, a recent study reported that A118G genotype moderates the effects of early maternal care on adult attachment style, with G allele carriers exhibiting high levels of fearful attachment regardless of the quality of their early maternal care (Troisi et al., 2012).

To examine the relevance of these findings for depression, we recruited 420 adolescents from a large longitudinal birth cohort study and followed them over time to assess their stress exposure and depression status. More specifically, we used a state-of-the-art, interview-based measure of life stress to identify whether participants experienced a major life event in the year prior to age 20, and standardized questionnaire and diagnostic interviewing methods to assess their levels of depression at ages 15 and 20. Finally, participants were genotyped for the A118G polymorphism in their early twenties. Consistent with the large body of research on life stress and depression (Hammen, 2005), we hypothesized that adolescents who experienced a major life event of any kind (i.e., targeted rejection or non-targeted rejection) in the year prior to age 20 would have more depressive symptoms, and a higher likelihood of meeting diagnostic criteria for MDD at age 20, compared to participants who did not experience such stress (i.e., controlling for relevant demographic and clinical factors). In addition, given prior research linking the G allele with heightened sensitivity to social rejection at the neural and psychological level (Way et al., 2009; Bertoletti et al., 2012), we hypothesized that these effects would be moderated by variation at the A118G locus, with G allele carriers exhibiting more stress-related depressive symptoms and higher rates of MDD following a recent major life event, relative to A/A homozygotes. Because endogenous opioids have been shown to specifically influence experiences of pain, however, we reasoned that moderation by A118G genotype would be unique to socially painful targeted rejection life events and not extend to other types of similarly severe major life stress (e.g., educational, financial, housing, health, crime events).