

Romantic Breakup Distress, Betrayal and Heartbreak: A Review

Review Article

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Abstract

A review of the romantic breakup literature suggests that it can lead to breakup distress, betrayal and heartbreak. The breakup distress that occurs can be explained in part by depression and feelings of rejection and betrayal. These may lead to physical problems including heartbreak or the broken heart syndrome and immune dysfunction. The broken heart syndrome has notably mimicked heart attacks, but it has been differentiated from a real heart attack by angiograms revealing unclogged arteries and no permanent heart damage. Reduced vagal activity and increased cortisol and catecholamine levels (dopamine and norepinephrine) accompanying heartbreak are thought to be potential underlying mechanisms for the broken heart syndrome and for immune dysfunction including increased inflammatory cytokines and reduced natural killer cells. fMRIs following breakups have revealed increased activity in the cingulate cortex and the right ventricular prefrontal cortex. These data highlight the complexity of breakup distress, betrayal and heartbreak and the need for multi-variable research.

This narrative review involved a literature search on the terms romantic breakup distress, betrayal and heartbreak on PubMed and PsycInfo. For the selection process, the inclusion criteria were: published empirical studies, systematic reviews and meta-analyses. Exclusion criteria included: non-English papers, case studies, under-powered samples, and non-juried papers. Following these screening criteria, the publications selected are briefly reviewed here.

Romantic Breakup Distress

Although romantic breakups, breakup distress and heartbreak are common among adults, they have occurred as early as the seventh grade [90], and most of the studies on these topics have been conducted with university students, as reflected by the literature reviewed in this paper. Romantic breakups occur in as many as two-thirds of university samples [43, 104]. The breakups frequently lead to breakup distress which is often associated with depression, feelings of rejection and betrayal, heartbreak symptoms including chest pain and compromised immune function. This review summarizes some of that literature.

In one of the early studies on romantic breakups in university students, the Breakup Distress Scale (adapted from the Inventory of Complicated Grief) and several other measures were used to assess the distress that followed romantic breakups [43]. In that, 192 university students (primarily Hispanic women) were surveyed about their recent romantic breakup. The students were divided

into high versus low scoring groups based on the Breakup Distress Scale. The group with high Breakup Distress Scale scores reported that they had less time since the breakup occurred, that they were not the initiators of the breakup, that the breakup was sudden and unexpected, and that they felt rejected and betrayed. In a regression analysis on the same database, the depression scores (CES-D) and feeling rejected and betrayed by the breakup were significant predictors of the Breakup Distress scores. These variables explained 37% of the variance, highlighting their relationships to breakup distress. These results were not surprising given that depression has been related to other kinds of grief, and feelings of rejection and betrayal have been notably similar to physical pain and have led to immune dysfunction [29, 47]. Thus, literature that related romantic breakups to depression, rejection and betrayal, pain and immune dysfunction are reviewed here. In addition, fMRI and biochemical data are reviewed as potential underlying mechanisms, and social and biochemical interventions are briefly explored.

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Depression

Breakup distress has frequently been associated with depression shortly before or during college [78]. Depression in university students is an increasing concern worldwide [12], ranging from an incidence of 6% in a Chinese survey [63] to 17% of students at a New Zealand university having depressive symptoms [116] and to 48% of those students at a U.S. university reporting clinically significant depressive symptomatology [21]. The most frequently symptoms expressed among the students were sleep problems, intrusive thoughts and difficulty concentrating. Another U.S. University Counseling Center reported an increase of 131% in yearly visits as well as a 173% increase in total yearly clients [13]. Thus, depressive symptoms are prevalent in university students, and they are associated with significant academic impairment [66, 71].

In a phone survey, romantic breakups were one of the most commonly reported “worst events” and they were a significant risk factor for depression [100]. In another study, over 40% of those experiencing romantic breakups became clinically depressed (12% experienced moderate to severe depression) [97].

Other predictors of depression in university students have included insecurity of attachment [74], perfectionism, and rumination [15, 73]. In a sample of 283 university students, those with high depression scores also had high scores on anxiety, intrusive thoughts, and sleep disturbance scales [45]. A stepwise regression suggested that those problems contributed to 51% of the variance on the depression scores. Two subscales of the depression scale that correlated most highly with these variables included the depressed affect and the vegetative symptoms subscales.

Women typically experience more severe depression and hopelessness following breakups, being twice as likely to be depressed as men [97]. However, men are three to four times more likely to commit suicide after romantic breakups. Depression, in turn, has been related to loneliness (an incidence of 35% for female university students and 24% for male students), and, here again, women had higher depression and loneliness scores [80]. Heart attacks and strokes can also follow breakups and depression [113].

Depression occurs more often in those who have been rejected versus those who initiated the rejection [6]. In those who are depressed, positron emission tomography (PET) scans suggest that rejection results in reduced opioid release in brain regions that regulate stress, mood and motivation and, in turn, to slower emotional recovery [70].

Rejection

Feeling rejected was the second predictor variable to contribute to the variance in the Field et al., [43] study on breakup distress. Rejection is often felt following breakups. In a survey at Case Western Reserve University, 95% of the students reported that they had rejected someone who was in love with them, and 93% said that they had been rejected by someone they loved [11]. Rejection following romantic relationships has been reputedly so painful that people report that they are “not only in agony, but incapacitated” [92].

Rejection following romantic breakups has been accompanied by

increased blood pressure and elevated stress hormone (i.e. cortisol) [126] and by analgesia or numbing [92]. Paradoxically, the same part of the brain that is activated by rejection is also activated by love [39]. Social rejection has also been simulated using the Cyberball paradigm (a social exclusion or inclusion condition in a virtual ball-tossing game), and increased heart rate has been noted following this “social rejection” condition [72].

Romantically rejected individuals have shown signs of drug withdrawal including anxiety, depression, crying, loss of appetite and irritability, and their fMRIs were similar to individuals withdrawing from cocaine or opioids [10]. Paradoxically, activation of endogenous opioid activity in the amygdala and anterior cingulate cortex (based on PET scans) is associated with the reduction of social rejection pain [70].

To address the question of why some people become depressed following socially painful rejection life events and some do not, a research team assessed recent rejection stress using self-reports and interviews, and the participants were also genotyped for the polymorphism of the opioid receptor gene [120]. The researchers found that carriers of the G allele, who typically exhibit less opioid expression and signaling, were more severely depressed following a recent rejection. These data suggest a potential underlying biological mechanism for sensitivity to rejection and social pain.

Betrayal

Feelings of betrayal often accompany feelings of rejection, and betrayal also entered the regression analysis on breakup distress in the Field et al., (2009) [43] study.

Betrayal has been defined as “...a sense of being harmed by the intentional actions or omissions of a person who was assumed to be a trusted and loyal friend, relative, partner, colleague or companion. Many betrayals are unexpected events that come as a surprising shock; not infrequently, the betrayal is disbelieved at first. The effects of a betrayal tend to be long-lasting, even permanent, and are well-remembered” [109]. Some symptoms of betrayal are distress, intrusive images and rumination [109]. Others have studied betrayal as the loss of “social provisions”, most especially the loss of attachment to and guidance from the betrayal partner [30]. In this study 91% of the participants lost social provisions from their partners following romantic betrayal.

In a study on university students, the level of betrayal was assessed by the closeness of the relationship [95]. Those with high betrayal that happened in close relationships had more symptoms of depression and PTSD. In another study [58], betrayal was measured by three scales including: 1) The Brief Betrayal Trauma Scale [57] that defines high levels of betrayal as occurring in a close relationship and low levels in a non-close relationship; 2) The Impact of Event Scale [69] that assesses symptoms of intrusion, avoidance and hyperarousal; and 3) the Trauma Symptom Checklist [41] that assesses symptoms related to depression, anxiety, sleep disturbance, dissociation and sexual problems [58]. In this study, the final path model from a structural equations analysis suggested that high levels of betrayal (that experienced in a close relationship) were predictive of all of the assessed factors including depression, anxiety, intrusions and avoidance [58]. In contrast, low

levels of betrayal (experienced with someone who was not close) were only minimally related to anxiety. The most common high level betrayal was being emotionally or psychologically mistreated for a significant length of time by someone close. Betrayal trauma indirectly affected symptoms of intrusion, avoidance, depression and anxiety via disturbed emotion regulation.

Similar symptoms were reported by Rachman (2010) [109], who also noted obsessive compulsive disorder (OCD) and posttraumatic stress disorder (PTSD) symptoms in those with high betrayal. These symptoms as well as physical health complaints have been reported by university undergraduate students experiencing betrayal [57]. Still others have suggested that betrayal can lead to borderline personality disorder [14].

Gender differences have been noted in the level of betrayal, suggesting that females were more likely to experience high levels of betrayal [95]. Others have reported that females (again university students) not only experienced higher levels of betrayal but also more PTSD symptoms [8]. These authors also noted that females experienced more betrayal in both childhood and adulthood, consistent with others' findings [57]. And, greater betrayal during childhood has been related to greater betrayal during adulthood [7].

Other factors include age and being a psychology major (Barlow & Cromer, 2006) [8]. These authors suggested that psychology majors experienced more low and high betrayal in childhood and more low betrayal in adulthood, and that current age was correlated with reporting betrayal regardless of whether it occurred in childhood or adulthood.

Other betrayal-related phenomena have been noted including that depressed individuals experiencing interpersonal betrayal become more critical of their personality characteristics and their performance on an experimental task than those who experienced a cooperative interaction [64]. In the same experiment, the depressed subjects in the betrayal condition behaved more aggressively toward their betraying partner. Betrayal aversion is another phenomenon. In an fMRI study the anterior insula became active during trusting decisions that involved the possibility of betrayal [2]. The authors suggested that "betrayal aversion" derives from the desire to avoid negative emotions that result from one's trust being betrayed.

Betrayal blindness has also been reported [76]. These authors suggest that in highly dependent relationships, the betrayed individual may be advantaged by "remaining unaware" of the betrayal rather than risking being alienated by the needed other. Forgetting or misremembering betrayal might also be adaptive [34]. Forgiveness of betrayal has been associated with commitment to the relationship [46]. In this study, commitment to a relationship was more likely to lead to forgiveness than to vengeance or bearing a grudge.

A growing literature on oxytocin and betrayal suggests the modulating effects of oxytocin. For example, in one study, oxytocin made females, but not males, less forgiving following betrayal of trust [139]. Even though oxytocin has been thought to enhance trust behavior, the females in this study exhibited more punitive behavior toward partners who violated their trust and were less sensitive to repair strategies. Females with a more forgiving attitude were more likely to punish betrayal. In a study on high at-

tachment-avoidant males, oxytocin that was administered intranasally decreased their betrayal aversion and enhanced their trust and cooperation compared to a placebo [33].

Oxytocin has increased and maintained trust even towards untrustworthy partners [81]. In this study, participants played a trust game involving the opponent betraying their trust, and oxytocin reduced the link between the anger and blaming the other person that usually follows betrayal. This might be explained by variations in the gene that encodes the oxytocin receptor [127]. In this study, one haplotype was associated with increased anger following betrayal, while another haplotype was associated with less anger.

Heartbreak (Broken Heart Syndrome)

Physical pain in the heart or chest after losing someone has been labeled heartbreak or the broken heart syndrome [136]. This acute pain has also been called stress cardiomyopathy or "takotsubo cardiomyopathy". Takotsubo is a fishing pot with a narrow neck and a wide base that is used to trap octopus in Japan, and the left ventricle of the heart looks like that fishing pot following heartbreak. Heartbreak has led to endocrine and immune dysfunction [56] and serious medical conditions including cancer, hypertension and heart attacks [125]. Although the heartache mimics symptoms of a heart attack, those with broken heart syndrome typically recover faster. Cardiac contractile abnormalities and heart failure have been recorded by several investigators following acute emotional stress [20, 85]. Angiograms, however, revealed no clogged arteries in heartbreak, unlike real heart attacks.

In addition, cardiac enzymes typically released from damaged heart muscle during real heart attacks have not been reported [136]. Although other heart changes associated with stress also occur including weakened contractions in the left middle and upper portions of the heart muscle and inverted T waves. These heart changes have been attributed to exaggerated sympathetic stimulation and elevated catecholamines including norepinephrine and epinephrine [135, 136].

The spasms in the coronary arteries may also relate to the increased catecholamines [136]. The spasm-related loss of blood flow could also lead to the transient stunning of the heart [85]. A failure of the arteries to provide adequate oxygen to the heart is another possibility [77]. Finally, all of these factors may be operating. Despite their heart attack symptoms, none of the broken heart syndrome patients suffered irreversible heart damage based on magnetic resonance imaging scans, and their recovery rates were typically two months faster than after real heart attacks [3]. Paradoxically, takotsubo cardiomyopathy has also followed a positive emotional event in a postmenopausal woman [4].

These data are tenuous at best given the mixed findings (i.e. both negative and positive events leading to the cardiomyopathy) and the small samples in these studies. Although increased heart rate and the release of catecholamines are correlated with the heartbreak symptoms, the relationships are only suggestive. Elevated catecholamines may be an epiphenomenon of the stress cardiomyopathy rather than the cause. The types of pain (acute, chronic, psychological, somatic) needs to be differentiated for the diagnosis to be more clearly made.

Reduced Vagal Activity

A potentially related problem is the decreased vagal tone following emotional stress, suggesting a sympathetically activated (aroused) state [50]. And, curiously, gastric activity is increased following emotional arousal [132]. These effects are difficult to interpret given that the vagus has a branch to the GI tract, and decreased vagal tone is typically expected to lead to decreased not increased gastric activity [35]. The expression “gut feelings” that is often used to describe emotional arousal may relate to the increased gastric activity.

Compromised Immune Function

Romantic breakups have been associated with extreme physical and emotional distress, exaggerated attempts to re-establish the relationship, angry and vengeful behavior, and drug and alcohol use based on a survey of more than 5,000 internet respondents [32]. In addition, increased stress hormones and disrupted sleep and immune function have been noted [119]. Cortisol dysregulation has been associated with sleep disturbances such as increased REM density [111], insomnia [55] and immune changes [1996]. Compromised immune function may result from the increased heart rate, blood pressure, cortisol and norepinephrine levels following heartbreak [130]. These physiological and biochemical reactions may initially be adaptive in increasing proinflammatory cytokines, and they, in turn, increase antibodies to prevent infection [18]. But if this response is prolonged, elevated stress hormones and cytokines can impair immune function [79]. For example, proinflammatory cytokines (IL-1, IL-2, IL-6 and TNF-alpha) accompany depression [86].

In a social rejection study, the social stressors were associated with increases in two markers of inflammatory activity including TNF-alpha and IL-6 [120]. Greater increases in TNF-alpha were also associated with greater activity in the dorsal anterior cingulate cortex and anterior insula, regions that have been reportedly affected by rejection-related distress. In a more recent study, heightened activation of the amygdala was associated with greater increases in inflammation [102]. Individuals who had a stronger coupling between the amygdala and the dorsomedial prefrontal cortex showed a greater inflammatory response to the stressor. Still another example of the inflammatory response is high antibody titres to the Epstein-Barr virus following divorce [108].

Decreases in natural killer cells (noted to kill bacterial, viral, and cancer cells) have also occurred in individuals who experienced loss and had high anxiety and depression scores and elevated cortisol [56]. Some of the participants had reduced natural killer cells for as long as six months. Other researchers have reported a greater incidence of illness [51] and heart disease [75] in individuals who have experienced loss.

Brain Activity Associated With Heartbreak

The anterior cingulate cortex has been noted to light up on fMRIs following rejection [39]. The cingulate cortex, the long ribbon of tissue at the brain's midline, has a region that is involved in negative emotions like rejection. In an fMRI study on bereaved women, for example, photographs of the lost person were used to elicit grief [62], and the posterior cingulate cortex was activated.

In another fMRI study, women who were grieving the loss of a romantic relationship showed similar regional brain activity [103].

In a computer game (Cyberball) study, the fMRIs of players who were excluded from the game showed that social rejection lit up the cingulate cortex very much like physical pain [106]. The anterior cingulate cortex was the critical site for physical pain signals in a study using PET scans [110]. Antidepressants have reduced the activity of the anterior cingulate [96] and they typically reduce pain as well [22]. Opioids such as morphine can regulate both physical and social pain [128].

The right ventral prefrontal cortex (RVPFC) has also been activated in response to rejection [39]. In a more recent study, the right ventral prefrontal cortex was also activated following social rejection [26]. The authors suggested that this activation led to a subsequent self-regulatory imbalance that led to reflexive impulses like daily cravings for alcohol.

Social Pain And Physical Pain Activate Similar Brain Regions

The same region (the right ventral prefrontal cortex) has been active in neuroimaging studies during painful stimulation [87, 106]. Greater RVPFC activation was associated with less pain. Because the RVPFC is involved in cognitive activities, its activation during pain suggests the therapeutic use of cognitive tasks to interrupt social pain. Cognitive tasks have been successful at least in reducing the impact of intrusive thoughts following rejection and loss. Thus, the underlying mechanisms common to physical and social pain include the location in the brain (the anterior cingulate cortex and the right ventral prefrontal cortex) and the opioid system [114].

Many of the neuroimaging studies that suggested that social rejection activated the pain matrix were Cyberball studies and small sample studies. A meta-analysis on the Cyberball studies, however, failed to support the claim that social and physical pain activate the same regions [23]. And, in a study in which participants experienced both physical pain (heat) and social pain (photos of ex-partners) on separate trials, the fMRI patterns discriminated the physical and social pain conditions, i.e. those conditions did not activate the same region (the anterior cingulate cortex) [137].

In contrast, in a study on recent unwanted break-ups, when the participants viewed a photograph of their ex-partner, even the sensory areas for physical pain were activated (the secondary somatosensory cortex and the dorsal posterior insula) [83]. Further, these authors compared their data to data from over 500 published studies on physical pain demonstrating that both social pain and physical pain activated these sensory regions. The authors suggested that these effects may have been elicited by more powerful, more recent and unwanted break-up experiences. Thus, the literature is very mixed on physical and social pain sharing neural systems [37].

fMRIs Of Rejected Love Are Similar To Those Of Romantic Love

The same brain areas that light up in long-term love relationships also light up in rejected relationships [48]. In this study, women

who were still in love with their rejecting partner viewed a photograph of their rejecting loved one and a photograph of a familiar individual interspersed with a counting task. Similar brain areas were activated for rejected lovers, although they showed greater activity in the ventral pallidum than the in-love sample. This region has been associated with uncertain reward and delayed reinforcement [25]. These data suggest that the brain systems involved in reward and motivation remain active in those who have been romantically rejected. The data also showed that activity in regions associated with physical pain increased during rejection. These findings are consistent with data showing similar biochemical profiles for romantic love and romantic rejection.

Rejected And Romantic Love Have Similar Biochemical And Physiological Profiles

Neuroscientists have reported that the brain releases similar chemicals for both rejected and romantic love including dopamine, norepinephrine, epinephrine and serotonin, which act like amphetamines in stimulating the brain's pleasure center [48]. As dopamine and norepinephrine levels increase, serotonin levels decrease [91]. Elevated dopamine and norepinephrine and low serotonin levels, as already mentioned, have been associated with both heartbreak and romantic love [48]. Other characteristics of heartbreak and romantic love have also been correlated with elevated dopamine including increased energy, sleeplessness, loss of appetite, a pounding heart, accelerated breathing and anxiety. Elevated norepinephrine has also accompanied excessive energy, sleeplessness and loss of appetite [61]. The dependency and cravings that are associated with both romantic love and rejection are symptoms of addiction, as already mentioned, and both romantic love and addictions are associated with elevated dopamine [1, 49, 118]. Romantic love has been associated with elevated dopamine and oxytocin, while addictions are more often associated with elevated dopamine [133]. The heartbreak experience may be similar to drug withdrawal, as in withdrawal from dopamine and oxytocin.

Low serotonin levels have also accompanied heartbreak and romantic love [48]. In that comparison between individuals who were in love and those who were not in love, the group in love had lower serotonin levels than the group not in love. Low serotonin may contribute to the ruminations that have been associated with both being in love and being rejected [48].

fMRI Studies Show Activation Of Dopaminergic Pathways

The biochemical findings just reviewed are not surprising given that the parts of the brain that are stimulated by both romantic love and heartbreak also release these chemicals. In an fMRI study, those who were in love were given fMRIs while viewing the photo of their loved one versus a photo of an acquaintance [5]. The photo of the loved one activated the caudate nucleus which was not surprising since the caudate nucleus is also involved in the reward system and the release of dopamine [107]. The caudate nucleus near the center of the brain is generally considered one of the brain's reward systems involved in pleasure, general arousal and motivation for rewards [118]. Other areas of the reward system including the septum are activated by love as well as by chocolate, both of which are thought to be addictive [121].

Other fMRI studies using the same paradigm (viewing a romantic lover) have revealed different findings. For example in an fMRI study, functional connectivity in the reward and emotion regulation network (the dorsal anterior cingulate cortex) was positively associated with length of time in love in the "in-love" group and negatively correlated with the duration since breakup in the "ended-love" group [122]. These inconsistencies highlight the need for additional fMRI studies that use similar experimental paradigms and imaging measures.

Protective Factors

Several protective factors have been discussed in the literature on break-up distress including personality characteristics such as self-esteem [82, 132], attachment style (secure versus anxious attachment) [16, 32], coping style [105], and rejection sensitivity [36, 84]. Other factors such as forgiveness [138], finding a new partner/rebound [123], social support [98], healthy diet [40], heartbreak songs [129], and ball sports and dancing [54] can mediate breakup distress. Finally, interventions, including cognitive behavioral therapy [19], intranasal oxytocin [89] and MDMA (3-4-Methylenedioxyamphetamine) [52] have been effective. A few examples of these are elaborated here.

Individuals with higher trait self-esteem have shown less distress after imagining a romantic rejection than after ending or imagining themselves ending their relationships [134]. In this study, university students were assessed following the end of their real-life romantic relationships as well as in a laboratory condition in which they were asked to imagine breaking up with their partners. Self-esteem was a mediating factor in another study along with attachment anxiety and covert narcissism [16]. In the first of two studies, emotional responses to a vignette on romantic rejection were assessed including self-reported mood states, anger, somatic symptoms, self-esteem and attachment style. Those with higher scores on attachment anxiety had stronger responses to the romantic rejection scenarios. In their second study (same publication) the same authors reported that higher scores on covert narcissism were also associated with stronger responses to the romantic rejection.

Attachment anxiety has been related to greater preoccupation and perseveration about romantic breakups, greater emotional and physical distress, extreme attempts to reinstate the relationship, and angry and vengeful behavior [32]. In this survey on more than 5,000 internet respondents, attachment anxiety was also related to drug and alcohol use, while those who were securely attached used more social coping strategies such as "using friends and family as 'safe havens'".

Paradoxically, greater breakup distress in individuals with an anxious attachment style has led to more personal growth [94]. In a structural equations analysis, the greater personal growth appeared to be mediated by "enhanced reflection and brooding.... and a proclivity to rebound". Posttraumatic growth has been frequently reported [24, 88].

In a series of studies, finding a new partner was a key factor in overcoming attachment to an ex-romantic partner by individuals with an anxious attachment style [123]. First, a correlational

study suggested that finding a new romantic partner disrupted the attachment to the ex-partner. Then, experimental manipulations inducing belief in finding a new partner effectively facilitated breakup recovery.

Cognitive behavior therapy has been notably effective in treating romantic breakups [19]. In addition, two drug treatments have been reputedly effective including intranasal oxytocin [89] and MDMA [52]. In the double-blind intranasal oxytocin study. The Yale Interpersonal Stressor, a live social rejection paradigm, was used with undergraduate students [89]. The students who received intranasal oxytocin versus those who received placebo showed a decrease in cortisol levels. In the MDMA study, MDMA versus placebo decreased the effects of simulated social rejection (Cyberball condition) on self-reported mood and self-esteem and decreased the perceived intensity of rejection [52]. MDMA also decreased respiratory sinus arrhythmia, as might be expected given its sympathomimetic properties.

Methodological Limitations

This review is based on separate literatures including research on romantic breakups, rejection, betrayal and the heartbreak syndrome. Much of the breakup literature is focused on romantic breakups and divorce. While these may have the commonalities of feelings of rejection and betrayal, divorce has the difference of having or not having to continue the relationship for family reasons. The heartbreak syndrome literature is mostly based on loss to death, making it difficult to compare to romantic breakups and divorce given the different durations of the relationships and depth/meaningfulness of the relationships. Even within the same type of loss literatures comparisons are difficult because of the different measures used, the different intervals from the time of loss to the time of the assessments and the different ethnic and age groups assessed.

Other problems are the small sample sizes and the limited number of variables measured. Multi-variable studies are needed especially to assess those paradoxical findings such as romantic breakups and romantic love yielding similar results on fMRIs and on biochemical measures. Optimally, self-report, behavioral, physiological and biochemical measures would be taken on the same samples.

Summary

In summary, the distress that occurs following romantic breakups is largely explained by depression, rejection and betrayal. These may lead to heartbreak or the broken heart syndrome and immune dysfunction. Although the broken heart syndrome mimics a real heart attack, it has been differentiated from heart attacks by angiograms revealing unclogged arteries and no permanent heart damage. Reduced vagal activity has been noted to accompany heartbreak, and increased cortisol and catecholamines are thought to lead to the associated immune dysfunction including increased inflammatory cytokines and decreased natural killer cell number. fMRIs reveal increased activity in the cingulate cortex and the right prefrontal ventricular cortex. These data highlight the complexity of breakup distress, rejection, betrayal and heartbreak and the need for multi-variable research.

Recommendations for Future Research

One of the most perplexing questions that needs to be addressed to inform the breakup/heartbreak literature is what aspects of the relationship are then missing when the breakups occur. Relationships have been viewed as regulators of stimulation so as not to be understimulated or overstimulated [42, 67, 117]. This has been called “psychobiological attunement”. Physical and emotional intimacy are also critical to relationships [44]. Most of the breakup distress studies are based on retrospective self-reports. Prospective studies are needed to capture the relationship variables that are lost following breakups. For example, the social interactions of university students could be videotaped during the relationship, and heart rate and cortisol levels could be assessed to provide more data on the features of the relationship that get interrupted by breakups, much like Gottman and Levenson (2002) [60] have done with married couples. These data might provide important information for designing interventions to alleviate the pain associated with the breakups that are so prevalent, especially among university students.

References

- Abbott A. Neuroscience: addicted. *Nature*. 2002 Oct 31;419(6910):872-878. PubMed PMID: 12410246.
- Aimone J, Houser D, Weber B. Neural signatures of betrayal aversion: an fMRI study of trust. *Proc Biol Sci*. 2014 Mar 19;281(1782): 20132127. PubMed PMID: 2468217.
- Akashi YJ, Nakazawa K, Sakakibara M, Miyake F, Koike H, Sasaka K. The clinical features of takotsubo cardiomyopathy. *QJM*. 2003 Aug;96(8):563-573. PubMed PMID: 12897341.
- Allen D, Parmar G, Ravandi A, Hussain F, Kass M. Happiness can break your heart: A rare case of takotsubo cardiomyopathy after good news. *Can J Cardiol*. 2015 Feb;31(2):228-230. PubMed PMID: 25661563. PubMed PMID: 25661563.
- Aron A, Fisher H, Mashek DJ, Strong G, Li H, Brown LL. Reward, motivation, and emotion systems associated with early-stage intense romantic love. *J Neurophysiol*. 2005 Jul;94(1):327-337. PubMed PMID: 15928068.
- Ayduk O, Downey G, Kim M. Rejection sensitivity and depressive symptoms in women. *Personal Soci Psychol Bull* 2001 Jul 1;27:868-877.
- Babcock R, Deprince A. Factors contributing to ongoing intimate partner abuse; childhood betrayal trauma and dependence on one's perpetrator. *J Interpersl Viol*. 2013 Dec 24;28:1385-402.
- Barlow M, Cromer L. Trauma-relevant characteristics in a university human subjects pool population: gender, major betrayal and latency of participation. *J Trauma Dissociation*. 2006;7(2):59-75. PubMed PMID: 16769666.
- Barry RA, Lawrence E, Langer A. Conceptualization and assessment disengagement in romantic relationships. *Pers Relatsh*. 2008 Sep;15(3):297-315. PubMed PMID: 19727315.
- Bartels A, Zeki S. The neural basis of romantic love. *Neuroreport*. 2000 Nov 27;11(17):3829-34. PubMed PMID: 11117499.
- Baumeister RF, Votman SR, Stillwell AM. Unrequited love: On heartbreak, anger, guilt, scriptlessness and humiliation. *J Pers Soci Psychol*. 1993;64(3):377-394.
- Bayram N, Bilgel N. The prevalence and socio-demographic correlations of depression, anxiety and stress among a group of university students. *Soc Psychiatry Psychiatric Epidemiol*. 2008 Aug;43(8):667-672. PubMed PMID: 18398558.
- Beiter R, Nash R, McCrady M, Rhoades D, Linscomb M, Clarahan M. The prevalence and correlates of depression, anxiety and stress in a sample of college students. *J Affect Disord*. 2015 Mar 1;173:90-96. PubMed PMID: 25462401.
- Belford B, Kaehler L, Birrell P. Relational health as a mediator between betrayal trauma and borderline personality disorder. *J Trauma Dissociation*. 2012;13(2):244-57. PubMed PMID: 22375810.
- Besharat M, Issazadegan A, Etemadnia M, Golssanamlou S, Abdolmafai A. Risk factors associated with depressive symptoms among undergraduate students. *Asian J Psychiatr*. 2014 Aug;10:21-26. PubMed PMID: 25042947.
- Besser A, Priel B. Emotional responses to a romantic partner's imaginary rejection: the role of attachment anxiety, covert narcissism and self-evaluation.

- J Pers. 2009 Feb;77(1):287-325. PubMed PMID: 19076997.
- [17]. Biondi M, Picardi A. Clinical and biological aspects of bereavement and loss-induced depression: a reappraisal. *Psychother Psychosom.* 1996;65(5):229-273. PubMed PMID: 8893324.
- [18]. Black PH. Stress and the inflammatory response: a review of neurogenic inflammation. *Brain Behav Immun.* 2002 Dec;16(6):622-635. PubMed PMID: 12480495.
- [19]. Boelen PA, de Keijser J, van den Hout MA, van den Bout J. Treatment of complicated grief: a comparison between cognitive-behavioral therapy and supportive counseling. *J Consult Clin Psychol.* 2007 Apr; 75(2):227-310. PubMed PMID: 17469885.
- [20]. Bounhoure J. Takotsubo or stress cardiomyopathy. *Cardiovasc Psych Neurol.* 2012;29:1-4. PubMed PMID: 637672.
- [21]. Brandy JM, Penckofer S, Solari-Twadell PA, Velsor-Friedrich B. Factors predictive of depression in first-year college students. *Journal Psychosocial Nursing Mental Health Services.* 2015 Feb;53(2):38-44. PubMed PMID: 25654575.
- [22]. Brown JL, Sheffield D, Leary MR, Robinson ME. Social support and experimental pain. *Psychosom Med.* 2003 Apr;65(2):276-283. PubMed PMID: 12651995.
- [23]. Cacioppo S, Frum C, Asp E, Weiss R, Lewis J, Cacioppo J. A quantitative meta-analysis of functional imaging studies of social rejection. *Sci Rep.* 2013 Jun;19:31-3.
- [24]. Calhoun LG, Tedeschi RG. The foundations of posttraumatic growth: An expanded framework. In: Calhoun LG, Tedeschi RG, editors. *The Handbook of posttraumatic growth: Research and practice.* Mahwah, NJ: Lawrence Erlbaum Associates. 2006;1-23.
- [25]. Cardinal RN, Howes NJ. Effects of lesions of the accumbens core on choice between small uncertain rewards in rats. *BMC Neuroscience.* 2005;6:37-56. PubMed PMID: 117798.
- [26]. Chester D, DeWall C. Prefrontal recruitment during social rejection predicts greater subsequent self-regulatory imbalance and impairment: neural and longitudinal evidence. *Neuroimage.* 2014 Nov 1;485-93. PubMed Central PMCID: PMC4170689.
- [27]. Coan JA, Schaefer HS, Davidson RJ. Lending a hand: social regulation of the neural response to threat. *Psychol Sci.* 2006 Dec;17(12):1032-1039. PubMed PMID: 17212784.
- [28]. Connelly J, McIsaac C. Adolescents' explanations for romantic dissolutions: A developmental perspective. *J Adolesc.* 32(5):1209-1223. PubMed PMID: 19232706.
- [29]. Corns J. The social pain posit. *Austral J Philo.* 2014 Nov 28;93(3):56-582.
- [30]. Couch L, Olson D. Loss through betrayal: An analysis of social provision changes and psychological reactions. *J Loss Trauma.* 2016;21(5): 372-383.
- [31]. Curcio G, Ferrara M, Gennaro L. Sleep loss, learning capacity and academic performance. *Sleep Med Rev.* 2006 Oct;10(5):323-337. PubMed PMID: 16564189.
- [32]. Davis D, Shaver PR, Vernon ML. Physical, emotional and behavioral reactions to breaking up: The roles of gender, age, emotional involvement, and attachment style. *Pers Soc Psychol Bull.* 2003 Jul;29, 871-884. PubMed ID: 15018675.
- [33]. De Dreu C. Oxytocin modulates the link between adult attachment and cooperation through reduced betrayal aversion. *Psychoneuroendocrinology.* 2012 Jul;37(7): 871-80.
- [34]. DePrince A, Brown L, Cheit R, Freyd J, Gold SN, Pezdek K, et al. Motivated forgetting and misremembering: Perspectives from betrayal trauma theory. *Nebr Symp Motiv.* 2012;58:193-242. PubMed PMID: 22303768.
- [35]. Diego M, Field T, Hernandez-Reif M, Deeds O, Ascencio A, Begert G. Pre-term infant massage consistently increases vagal activity and gastric motility that are associated with greater gain. *Acta Paediatr.* 2007 Nov;96(11):1588-1591. PubMed PMID: 1788059.
- [36]. Downey G, Freitas AL, Michaelis B, Khouri H. The self-fulfilling prophecy in close relationships: Rejection sensitivity and rejection by romantic partners. *J Pers Soc Psychol.* 1998 Aug;75(2):545-560. PubMed PMID: 17888059.
- [37]. Eisenberger N. Social pain and the brain: controversies, questions, and where to go from here. *Ann Rev Psychol.* 2015 Jan;66:601-29. PubMed PMID: 25251482.
- [38]. Eisenberger N, Lieberman M. Why rejection hurts: A common neural alarm system for physical and social pain. *Sci.* 2004 Jul;8(7):294-300. PubMed PMID: 15242688.
- [39]. Eisenberger N, Lieberman M, Williams K. Does rejection hurt? An fMRI study on social exclusion. *Sci.* 2003 Oct 10;302(5643): 290-292. PubMed PMID: 14551436.
- [40]. El Ansari W, Adetunji H, Oskrochi R. Food and mental health: relationship between food and perceived stress and depressive symptoms among university students in the United Kingdom. *Cent Eur J Public Health.* 2014 Jun;22(2):90-97. PubMed PMID: 25230537.
- [41]. Elliott D, Briere J. Sexual abuse trauma among professional women: Validating the Trauma Symptom Checklist-40. *Child Abuse and Neglect.* 1992;16(3):391-398. PubMed PMID: 1617473.
- [42]. Field T. Attachment as psychobiological attachment: Being on the same wavelength. In: Reite M, Field T, editors. *Psychobiol Attac.* New York: Academic Press; 1985.
- [43]. Field T, Diego M, Pelaez M, Deeds O, Delgado J. Breakup Distress in University Students. *Adolescence.* 2009;44(176):705-727. PubMed PMID: 20432597.
- [44]. Field T, Diego M, Pelaez M, Deeds O, Delgado J. Breakup Distress and the Loss of Intimacy in University Students. *Psychol.* 2010 Aug;1:173-177.
- [45]. Field T, Dieg. M, Pelaez, M, Deeds Delgado J. Depression and related problems in university students. *College Student J.* 2012;46:193-202.
- [46]. Finkel E, Rusbult C, Kumashiro M, Hannon P. Dealing with betrayal in close relationships: does commitment promote forgiveness? *J Pers Soc Psychol.* 2002;82(6):956-74.
- [47]. Fisher H. *Why We Love: The Nature and Chemistry of Romantic Love.* New York: Henry Holt; 2004.
- [48]. Fisher HE, Aron, A, Brown L. Romantic love: a mammalian brain system for mate choice. *Philos Trans R Soc Lond B Biol Sci.* 2006 Dec 29; 361(14776):2173-86. PubMed Central PMCID: 1764845.
- [49]. Fisher H, Xu X, Araon A, Brown L. Intense, passionate, romantic love: A natural addiction? How the fields that investigate romance and substance abuse can inform each other. *Front Psychol.* 2016 May 10;7:687-689. PubMed PMID: 27242601.
- [50]. Frazier TW, Strauss ME, Steinhauer SR. Respiratory sinus arrhythmia as an index of emotional response in young adults. *Psychophysiol.* 2004 Jan;41(1):75-83. PubMed PMID: 14693002.
- [51]. Freyd JJ, Klest B, Allard CB. Betrayal trauma: relationship to physical health, psychological distress, and a written disclosure intervention. *J Trauma Dissociation.* 2005;6(3):83-104. PubMed PMID: 16172083.
- [52]. Frye C, Wardle M, Norman G, deWit H. MDMA decreases the effects of simulated social rejection. *Pharmacol Biochem Behav.* 2014 Feb;117:1-6. PubMed PMID: 24316346.
- [53]. George MS, Ketter TA, Parekh PI, Herscovitch P, Post RM. Gender differences in regional cerebral blood flow during transient self-induced sadness or happiness. *Biological Psychiatry.* 1996 Nov 1;40(9):859-871. PubMed PMID: 8896772.
- [54]. Gerber M, Brand S, Elliot C, Holsboer-Trachsler E, Puhse U. Aerobic exercise, ball sports, dancing and weight lifting as moderators of the relationship between stress and depressive symptoms: an exploratory cross-sectional study with Swiss university students. *Perception and Motor Skills.* 2014 Dec;119(3):679-97. PubMed PMID: 25350930.
- [55]. Germain A, Caroff K, Buysse DJ, Shear MK. Sleep quality in complicated grief. *Traumatic Stress J.* 2005 Aug;18(4):343-346. PubMed PMID: 16281231.
- [56]. Gerra G, Monti D, Panerai A, Sacerdote P, Anderlini R, Avazini P, et al. Long-term immune-endocrine effects of bereavement: Relationships with anxiety levels and mood. *Psychiatry Res.* 2003 Dec 1;121(2):145-158. PubMed PMID: 14656449.
- [57]. Goldberg L, Freyd J. Self-reports of potentially traumatic experiences in an adult community sample: gender differences and test-retest stabilities of the items in a brief betrayal-trauma survey. *J Trauma Dissociation.* 2006;7(3):39-63. PubMed PMID: 16873229.
- [58]. Goldsmith R, Chesney S, Heath N, Barlow M. Emotion regulation difficulties mediate associations between betrayal trauma and symptoms of posttraumatic stress, depression and anxiety. *J Trauma Stress.* 2013 Jun;26(3):376-84. PubMed PMID: 23737296.
- [59]. Goldsmith R, Freyd J, DePrince A. Betrayal trauma: associations with psychological and physical symptoms in young adults. *J Interpers Viol.* 2012 Feb;27(3):547-67. PubMed PMID: 21987504.
- [60]. Gottman J, Levenson R. A two-factor model for predicting when a couple will divorce: exploratory analyses using 14-year longitudinal data. *Fam Process.* 2002 Spring;41(1):83-96. PubMed PMID: 11924092.
- [61]. Griffin MG, Taylor GT. Norepinephrine modulation of social memory: evidence for a time-dependent functional recovery of behavior. *Behav Neurosci.* 1995 Jun;109(3):466-538. PubMed PMID: 7662157.
- [62]. Gündel H, O'Connor MF, Littrell L, Fort C, Lane R. Functional neuroanatomy of grief: An fMRI study. *Am J Psychiatry.* 2003 Nov;160(11):1946-1953. PubMed PMID: 14594740.
- [63]. Guo L, Deng J, He Y, Deng X, Huang J, Huang G, et al. Prevalence and correlates of sleep disturbance and depressive symptoms among Chinese adolescents: a cross-sectional survey. *BMJ Open.* 2014 Jul 29; 4(7):e005517. PubMed PMID: 25079937.
- [64]. Haley W, Strickland B. Interpersonal betrayal and cooperation: effects on self-evaluation in depression. *J Pers Soc Psychol.* 50(2):386- 91. PubMed PMID: 3701585.

- [65]. Helgeson VS, Reynolds KA, Tomich PL. A meta-analytic review of benefit finding and growth. *J Consult Clin Psychol.* 2006 Oct;74(5): 797-816. PubMed PMID: 17032085.
- [66]. Hill R, Yaroslavsky I, Pettit J. Enhancing depression screening to identify college students at risk for persistent depressive symptoms. *J Affect Disord.* 2015 Mar 15;174:1-6. PubMed PMID: 25437632.
- [67]. Hofer MA. Relationships as regulators: A psychobiologic perspective on bereavement. *Psychosom Med.* 1984 Jun;46(3):183-197. PubMed PMID: 6739679.
- [68]. Holm-Hadulla R, Soeder U. Psychological complaints and disorders of students. *Psychother Psychosom Med Psychol.* 1997 Dec;47(12):419-425. PubMed PMID: 9471632.
- [69]. Horowitz MJ, Siegel B, Holen A, Bonanno GA, Milbrath C, Stinson CH. Diagnostic criteria for complicated grief disorder. *Am J Psychiatry.* 1997 Jul;154(7):4-10. PubMed PMID: 9210739.
- [70]. Hsu D, Sanford B, Meyers KI, Love TI, Hazlett K, Walker S, et al. It still hurts: altered endogenous opioid activity in the brain during social rejection and acceptance in major depressive disorder. *Mol Psychiatry.* 2015 Feb;20(2):193-200. PubMed Central PMCID: PMC4469367.
- [71]. Hysenbegasi A, Hass SL, Rowland CR. The impact of depression on the academic productivity of university students. *J Ment Health Policy Econ.* 2005 Sep;8(3):145-151. PubMed PMID: 16278502.
- [72]. Iffland B, Sansen L, Catani C, Neuner F. Rapid heartbeat but dry palms: reactions of heart rate and skin conductance levels to social rejection. *Front Psychol.* 2014 Aug 29;5:956. PubMed PMID: 25221535.
- [73]. Ito T, Takenaka K, Tomita T, Agari I. Comparison of ruminative responses with negative rumination as a vulnerability factor for depression. *Psychol Rep.* 2006;99(3):101-118. PubMed PMID: 17305194.
- [74]. Joel S, MacDonald G, Shimotomai A. Conflicting pressures on romantic relationship commitment for anxiously attached individuals. *J Pers.* 2011 Feb;79(1):51-73. PubMed PMID: 21223264.
- [75]. Johnson AK, Grippo AJ. Sadness and broken hearts: Neurohumoral mechanisms and co-morbidity of ischemic heart disease and psychological depression. *J Physiology Pharmacol.* 2006 Nov;57 Supp 11:529-534. PubMed PMID: 17244936.
- [76]. Johnson-Freyd S, Freyd J. Revenge and forgiveness or betrayal blindness? *Behav Brain Sci.* 2013 Feb;36(1):23-4. PubMed PMID: 23211413.
- [77]. Kawai S, Suzuki H, Yamaguchi H, Tanaka K, Sawada H, Aizawa T, et al. Ampulla cardiomyopathy ('Takotsubo' cardiomyopathy)—reversible left ventricular dysfunction with ST segment elevation. *Jpn Circ J.* 2000 Feb;64(2):156-159. PubMed PMID: 10716533.
- [78]. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry.* 2005 Jun;62(6):593-602.
- [79]. Kiecolt-Glaser JK, McGuire L, Robles TF, Glaser R. Emotions, morbidity, and mortality: New perspectives from psychoneuroimmunology. *Ann Rev Psychol.* 2002;53:83-107.
- [80]. Kim O. Sex differences in social support, loneliness, and depression among Korean college students. *Psychol Rep.* 2001 Apr;88(2):521-526. PubMed PMID: 11351902.
- [81]. Klack J, Pfundmair M, Agroskin D, Jonas E. Who is to blame? Oxytocin promotes nonpersonalistic attributions in response to a trust betrayal. *Biol Psychol.* 2013 Feb;92(2):387-94. PubMed PMID: 23201035.
- [82]. Knee CR, Canevello A, Bush AL, Cook A. Relationship-contingent self-esteem and the ups and downs of romantic relationships. *J Pers Soc Psychol.* 2008 Sep;95(3):608-627. PubMed PMID: 18729698.
- [83]. Kross E, Berman B, Mischel W, Smith E, Wager T. Social rejection shares somatosensory representations with physical pain. *Proc Natl Acad Sci USA.* 2011 Feb 22;108(15):6270-5.
- [84]. Kross E, Egner T, Ochsner K, Hirsch J, Downey G. Neural dynamics of rejection sensitivity. *J Cogn Neurosci.* 2007 Jun;19(6):945-956. PubMed PMID: 17536965.
- [85]. Kurisu S, Sato H, Kawagoe T, Masaharu I, Yuji S, Kenji N, et al. Tako-Tsubo-like left ventricular dysfunction with ST-segment elevation: A novel cardiac syndrome mimicking acute myocardial infarction. *Am Heart J.* 2002 Mar;143(3):448-455. PubMed PMID: 11868050.
- [86]. Leonard B. HPA and immune axes in stress: involvement of the serotonergic system. *Neuroimmunomodulation.* 2006;13(5-6):268-276. PubMed PMID: 17709948.
- [87]. Lieberman M, Jarcho J, Berman S, Naliboff B, Suyenobu B, Mandelkern M, et al. The neural correlates of placebo effects: a disruption account. *Neuroimage.* 2004 May;22(1):447-455. PubMed PMID: 15110038.
- [88]. Linley PA, Joseph S. Positive change following trauma and adversity: A review. *J Trauma Stress.* 2004 Feb;17(1):11-21. PubMed PMID: 15027788.
- [89]. Linnen A, Ellenbogen M, Cardoso C, Joobor R. Intranasal oxytocin and salivary cortisol concentrations during social rejection in university students. *Stress.* 2012 Jul;15(4):393-402. PubMed PMID: 22044077.
- [90]. Low N, Dugas E, O'Laughlin E, Rodriguez D, Contreras G, Chaiton M, et al. Common stressful life events and difficulties are associated with mental health symptoms and substance use in young adolescents. *BMC Psychiatry.* 2012;12:116. PubMed Central PMCID: PMC3466152.
- [91]. Luciana M, Collins PF, Depue RA. Opposing roles for dopamine and serotonin in the modulation of human spatial working memory functions. *Cerebral Cortex.* 1998 May; 8(3):218-244. PubMed PMID: 9617916.
- [92]. MacDonald G, Leary MR. Why does social exclusion hurt? The relationship between social and physical pain. *Psychol Bull.* 2005 Mar;131(2):202-223. PubMed PMID: 15740417.
- [93]. MacDonald G, Shaw S. Adding insult to injury: social pain theory and response to social exclusion. In: Williams KD, Forgas JP, Hippiel WV, editors. *The Social Outcast: Ostracism, Social Exclusion, Rejection, and Bullying*. Cambridge, England: Cambridge University Press; 2005.
- [94]. Marshall TC, Bejanyan K, Ferenczi N. Attachment styles and personal growth following romantic breakups: the mediating roles of distress, rumination and tendency to rebound. *PLoS One.* 2013;8(9):e75161. PubMed Central PMCID: PMC3774645.
- [95]. Martin C, Cromer L, Deprince A, Freyd J. The role of cumulative trauma, betrayal, and appraisals in understanding trauma symptomatology. *Psycholo Trauma.* 2013 Mar 1;5(2):110-118. PubMed Central PMCID: PMC3608140.
- [96]. Mayberg HS, Silva J, Brannan S, Tekell J, Mahurin R, Mc Ginnis, et al. The functional neuroanatomy of the placebo effect. *Am J Psychiatry.* 2002 May;159(5):728-737. PubMed PMID: 11986125.
- [97]. Mearns J. Coping with a breakup: Negative mood regulation expectancies and depression following the end of a romantic relationship. *J Pers Soc Psychol.* 1991 Feb;60(2):327-34. PubMed PMID: 2016673.
- [98]. Moller NP, Fouladi RT, McCarthy CJ, Hatch KD. Relationship of attachment and social support to college students' adjustment following a relationship breakup. *J Counsel Dev.* 2003 Jul;81(3):354-369.
- [99]. Monk TH, Houck PR, Shear MK. The daily life of complicated grief patients—what gets missed, what gets added? *Death Stud.* 2006;30(1):77-85.
- [100]. Monroe SM, Rohde P, Seeley JR, Lewinsohn PM. Life events and depression in adolescence: Relationship loss as a prospective risk factor for first onset of major depressive disorder. *J Abnorm Psychol.* 1999 Nov;108(4):606-614. PubMed PMID: 10609425.
- [101]. Murray SL, Holmes JG, MacDonald G, Ellsworth PC. Through the looking glass darkly? When self-doubts turn into relationships insecurities. *J Pers Soci Psychol.* 1998 Dec;75(6):1459-1480. PubMed PMID: 9914664.
- [102]. Muscatell K, Dedovic K, Slavch G, Jarcho M, Breen E, Bower J, et al. Greater amygdala activity and dorsomedial prefrontal-amygdala coupling are associated with enhanced inflammatory responses to stress. *Brain Behav Immun.* 2015 Jan;43:46-53.
- [103]. Najib A, Lorberbaum JP, Kose S, Bohning DE, George MS. Regional brain activity in women grieving a romantic relationship breakup. *Am J Psychiatry.* 161(12):2245-2256. PubMed PMID: 15569896.
- [104]. Oliveria ML, DantasCde R, Azevedo RC, Banzato CE. Demographics and complaints of university students who sought help at a campus mental health service between 1987 and 2004. *Sao Paulo Med J.* 2008; Jan 2;126(1):58-62. PubMed PMID: 18425289.
- [105]. Perilloux C, Buss DM. Breaking up romantic relationships: Costs experienced and coping strategies deployed. *Evol Psychol.* 2008 Jan 1; 164-181.
- [106]. Petrovic P, Petersson KM, Ghatan PH, Stone-Elander S, Ngar, M. Pain-related cerebral activation is altered by a distracting cognitive task. *Pain.* 2000 Mar;85(1-2):19-30. PubMed PMID: 10692599.
- [107]. Pfaff DW. *Drive: neurobiological and molecular mechanisms of sexual motivation.* Cambridge, MA: MIT Press; 1999.
- [108]. Powell LH, Loyaldo WR, Matthews KA, Meyer P, Midgley AR, Baum A, et al. Physiologic markers of chronic stress in premenopausal, middle-aged women. *Psychosom Med.* 2002 Jun;64(3):502-509. PubMed PMID: 12021424.
- [109]. Rachman S. Betrayal: A psychological analysis. *Behav Res Ther.* 2010 Apr;48(4):304-311. PubMed PMID: 20035927.
- [110]. Rainville P, Duncan GH, Price DD, Carrier B, Bushnell MD. Pain affect encoded in human anterior cingulate but not somatosensory cortex. *Sci.* 1997 Aug 15;277(5328):968-971. PubMed PMID: 9252330.
- [111]. Reynolds CF, Hoch CC, Guber DJ, Houck PR, Schleritzauer M, Frank E, et al. Electroencephalographic sleep in spousal bereavement and bereavement-related depression of late life. *Biol Psychiatry.* 1992 Jan 1;31(1):69-82.
- [112]. Rodriguez IA, Montgomery M, Pelaez M, Salas MW. Love attitudes and dating experiences of adolescents in three different cultures. *Mex J Psychol.* 2003;20:2-22.
- [113]. Rosenthal NE. *The Emotional Revolution: How the New Science of Feelings Can Transform Your Life.* New York: Citadel Press Books; 2002 Mar 1.
- [114]. Rotge J, Lemog, C, Hinfray S, Huguet P, Grynszpan O, Tartour E, et al. A

- meta-analysis of the anterior cingulate contribution to social pain. *Soc Cogn Affect Neurosci*. 2015 Jan;10(1):19-27. PubMed PMID: 4994851.
- [115]. Rudolph KD, Conley CS. The socioemotional costs and benefits of social-evaluative concerns: Do girls care too much. *J Pers*. 2005 Feb; 73(1):115-137. PubMed PMID: 15660675.
- [116]. Samaranyake C, Arroll B, Fernand A. Sleep disorders depression, anxiety and satisfaction with life among young adults: a survey of university students in Auckland, New Zealand. *N Z Med J*. 2014 Aug 1;127(1399):13-22. PubMed PMID: 25145302.
- [117]. Sbarra DA, Hazan C. Coregulation, dysregulation, self-regulation: an integrative analysis and empirical agenda for understanding adult attachment, separation, loss, and recovery. *Pers Soc Psychol Rev*. 2008 May;12(2):141-167. PubMed PMID: 18453476.
- [118]. Schultz W, Dayan P, Montague PR. A neural substrate of prediction and reward. *Sci*. 1997 Mar 14;275(5306):1593-1598. PubMed PMID: 9054347.
- [119]. Shear K, Shair H. Attachment, loss, and complicated grief. *Dev Psychobiol*. 2005 Nov;47(3):253-319. PubMed PMID: 16252293.
- [120]. Slavich G, Way B, Eisenberger N, Taylor S. Neural sensitivity to social rejection is associated with inflammatory responses to social stress. *Proc Natl Acad Sci USA*. 2010 Aug 17;107(33):14817-22. PubMed PMID: 2930449.
- [121]. Small DM, Zatorre RJ, Dagher A, Evans AC, Jones-Gotman M. Changes in brain activity related to eating chocolate: from pleasure to aversion. *Brain*. 2001 Sep;124(Pt 9):1720-1752. PubMed PMID: 11522575.
- [122]. Song H, Zou Z, Kou J, Liu Y, Yang L, Zilverstand A, et al., Love-related changes in the brain: A resting-state functional magnetic resonance imaging study. *Front Hum Neurosci*. 2015 Feb 13;9:71-74. PubMed PMID: 25762915.
- [123]. Spielmann S, Macdonald G, Wilson A. On the rebound: focusing on someone new helps as individuals let go of ex-partners. *Per Social Psychol Bull*. 2009 Oct;35(10):1382-94. PubMed PMID: 19625631.
- [124]. Starr LR, Davila J. Excessive reassurance seeking, depression, and interpersonal rejection: A meta-analytic review. *J Abnorm Psychol*. 2008 Nov;117(4):762-775. PubMed PMID: 19625631.
- [125]. Stroebe M, Schut H. The dual process model of coping with bereavement: Rationale and description. *Death Stud*. 1999 May;23(3):197-224. PubMed PMID: 10848151.
- [126]. Stroud LR, Tanofsky-Kraff M, Wilfley DE, Salovey P. The Yale Interpersonal Stressor (YIPS): affective, physiological, and behavioral responses to a novel interpersonal rejection paradigm. *Ann Behav Med*. 2000 May;204-213. PubMed PMID: 11126465.
- [127]. Tabak B, McCullough M, Carver C, Pedersen EC, Cuccaro M. Variation in oxytocin receptor gene (OXTR) polymorphism is associated with emotional and behavioral reactions to betrayal. *Soci Cogn Affect Neurosci*. 2014 Jun;9(6): 810-16. PubMedCentral PMCID: 4040089.
- [128]. Taylor S, Dickerson S, Klein L. Toward a biology of social support. 2nd ed. In: Snyder CR, Lopez SJ, Editors. *Handbook of positive psychology*. London, UK: Oxford University Press; 2002.
- [129]. Tsai CG, Chen RS, Tsa TS. The arousing and cathartic effects of popular heartbreak songs as revealed in the physiological responses of listeners. *Musicae Scientiae*. 2014 July 15;18(4):410-422.
- [130]. Uchino B, Kiecolt-Glaser J, Glaser R. *Psychological modulation of cellular immunity*. In: Cacioppo JT, Tassinari LG, Berntson GG, editors. *Handbook of psychophysiology*. New York: Cambridge University Press; 2000.
- [131]. Uvnäs-Moberg K. Oxytocin may mediate the benefits of positive social interaction and emotions. *Psychoneuroendocrinology*. 1998 Nov;23(8):819-835. PubMed PMID: 9924739.
- [132]. Vienna E, Tranel D. Gastric myoelectrical activity as an index of emotional arousal. *Int J Psychophysiol*. 2006 Jul;61(1):70-76. PubMed PMID: 16403424.
- [133]. Zuo Z, Song H, Zhang Y, Zhang X. Romantic love vs. drug addiction may inspire a new treatment for addiction. *Front Psychol*. 2016;7:1436. PubMed Central PMCID: PMC5031705.
- [134]. Waller K, MacDonald. Trait self-esteem moderates the effect of initiator status on emotional and cognitive responses to romantic relationship dissolution. *J Pers*. 2010 Aug 1;78(4):1271-99. PubMed PMID: 20545823.
- [135]. Wittstein IS. Stress cardiomyopathy: a syndrome of catecholamine-mediated myocardial stunning? *Cell Mol Biol*. 2012 Jul;32(5):847-57. PubMed PMID: 22297544.
- [136]. Wittstein LS, Thiemann DR, Lima J, Baughman KT, Schulman SP, Gerstenblith G, et al. Neurohumoral features of myocardial stunning due to sudden emotional stress. *N Engl J Med*. 2005 Feb 10;352(6):539-547. PubMed PMID: 15703419.
- [137]. Woo C, Koban L, Kross E, Lindquist M, Banich M, Ruzic L, et al. Separate neural representations for physical pain and social rejection. *Nat Commun*. 2014 Nov 17;5:5380-88. PubMed PMID: 25400102.
- [138]. Worthington EL, Witvliet CV, Pietrini P, Miller AJ. Forgiveness, health, and well-being: a review of evidence for emotional versus decisional forgiveness, dispositional forgiveness and reduced unforgiveness. *J Behav Med*. 2007 Aug; 30(4):291-302. PubMed PMID: 17453329.
- [139]. Yao S, Zhao W, Cheng R, Geng Y, Luo , Kendrick, K. Oxytocin makes females, but not males, less forgiving following betrayal of trust. *Int J Neuropsychol*. 2014 Nov;17(11):1785-92.