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The Neurochemistry of Heartbreak

Evidence, Mechanisms, and Limits of the Withdrawal Hypothesis

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Abstract

Purpose. Popular and secondary accounts often describe heartbreak as drug withdrawal: deprived of a partner who had become its "supply" of dopamine and oxytocin, the brain enters a neurochemical crash. This paper evaluates that account as a hypothesis. **Approach.** It reviews neuroimaging of romantic love and rejection, the oxytocin, vasopressin, serotonin and opioid literatures, stress physiology after separation, stress (takotsubo) cardiomyopathy, the debate over whether social and physical pain share neural representations, and longitudinal research on recovery, grading each central claim on a five-level evidence scale. **Position.** Reward-related brain regions respond to images of a rejecting partner, separation can disrupt stress physiology, and partner bereavement is followed by a short-term rise in cardiovascular risk. These findings support a weak version of the withdrawal hypothesis, in which romantic loss recruits motivational and learning systems that also figure in addiction. They do not support a strong version in which heartbreak *is* withdrawal, specific neurotransmitters are depleted, or chemical states cause the experience. Human evidence rests on small samples, peripheral hormone measures of doubtful validity, and inference from regional activation to mental states. Most people recover without intervention, and self-concept clarity, rumination and continued monitoring of the former partner are better studied correlates of recovery than any neurochemical marker. **Limits.** Samples are mostly young, Western and heterosexual, and causal human evidence is scarce. The paper closes with implications for preventive education, guidance on when to seek clinical care, ethical considerations, and a research agenda.

Keywords: *romantic rejection; attachment; dopamine; oxytocin; stress physiology; recovery*

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1. Introduction

The end of a valued romantic relationship is a common and often painful event in adolescence and adulthood, and a perennial subject of art, folk psychology and, more recently, neuroscience. Within popular writing about the brain, one framing has become especially common: heartbreak is "withdrawal." On this account, early love floods the brain with dopamine, bonding releases oxytocin and vasopressin, obsessive thoughts reflect lowered serotonin, and a breakup therefore produces a cascade of chemical deficits: a dopamine crash, an oxytocin collapse, a cortisol spike, an endorphin shortfall. It is further said that heartbreak is a measurable and predictable neurological injury, that men suffer a distinctive, testosterone-masked delayed collapse, and that recovery requires structured neurochemical intervention.

The framing has real appeal: it validates the intensity of grief after a breakup and connects a common experience to a large literature on reward and motivation. It also shows errors common in popular neuroscience: it equates neurotransmitters with feelings, treats correlations from small imaging studies as mechanisms, extrapolates from rodents to humans without qualification, overstates sex differences, and implies that a biological description licenses a biological fix.

This paper, the second in the Institute for Human Evolution (IHE) whitepaper series, evaluates the withdrawal framing as a scientific hypothesis: what the evidence shows about the neurobiology of romantic attachment and loss, where it is strong or weak, and what follows for education about relationship loss. It builds on the multilevel framework of IHE-WP-01, which places biological, psychological, dyadic and sociocultural explanations side by side.

1.1 Scope and definitions

The series uses *seduction* as an umbrella term for consensual, communicative behavior by which one person seeks to elicit or increase another person's romantic or sexual interest. Coercion, deception about material facts, harassment and attempts to influence a person who has not consented fall outside that definition and are not treated anywhere in the series as skills to be improved. This paper concerns the other end of the relationship arc: what happens when a romantic bond ends.

Heartbreak is used here as an everyday term, not a diagnosis, for the distress responses that follow the loss of a romantic relationship through rejection, mutual dissolution or a partner's death. *Romantic rejection* is the case in which one partner ends a relationship the other wished to continue. *Grief* is the normative emotional response to loss, including yearning, sadness and preoccupation with the lost person. *Major depressive disorder* is a clinical diagnosis with defined criteria of severity, duration and impairment; it overlaps with grief in symptoms but is distinct (Section 6.2).

Several neurobiological terms recur. The *mesolimbic dopamine system* comprises dopamine neurons in the ventral tegmental area (VTA) of the midbrain and their projections to the ventral striatum, including the nucleus accumbens. *Oxytocin* and *arginine vasopressin* are hypothalamic neuropeptides that act both as hormones in the bloodstream and as signaling molecules in the brain. The

hypothalamic-pituitary-adrenal (HPA) axis is the hormonal cascade that ends in cortisol release. *Functional magnetic resonance imaging (fMRI)* measures the blood-oxygen-level-dependent (BOLD) signal, an indirect hemodynamic correlate of neural activity; it does not measure neurotransmitters. *Positron emission tomography (PET)* with selective radiotracers can estimate receptor availability for specific neurochemical systems.

The *withdrawal hypothesis* has two forms. The **strong form** holds that heartbreak is withdrawal in the pharmacological sense: the partner functions like a drug, the brain becomes dependent on the neurochemicals the partner elicits, and the distress of loss is caused by their deficit. The **weak form** holds that the motivational and learning systems recruited by romantic attachment overlap with those recruited by addictive drugs, so that some features of loss (craving, cue-triggered intrusions, compulsive checking) can be usefully analyzed with concepts from addiction research. The paper argues that the evidence supports the weak form, within stated limits, and not the strong form.

1.2 Evidence-strength vocabulary

Every central empirical claim is graded with the following terms, used consistently across the IHE series:

- **Established:** replicated across laboratories, convergent methods, and large-sample or meta-analytic evidence.
- **Supported:** consistent findings, but with limited replication, limited samples, or reliance on a narrow set of methods.
- **Preliminary:** few or small studies, or a single method.
- **Contested:** credible evidence on more than one side, or failed replications of an initial finding.
- **Speculative:** a plausible hypothesis without direct evidence.

What this paper does not claim

It does not claim that heartbreak is a brain injury, a disease, or a form of drug addiction. It does not claim that any specific neurotransmitter or hormone causes the feelings of heartbreak, or that measuring one would diagnose or predict anyone's recovery. It does not recommend any drug, supplement, hormone, or physiological "reset" for heartbreak, and nothing in it should be read as medical advice. It does not claim that men and women, or people of different sexual orientations, have categorically different neurochemical responses to loss. It does not report original data. IHE is a young institute that provides preventive education, not treatment; it does not diagnose and refers people who need clinical care to licensed clinicians.

2. Methodological cautions

Five problems run through this literature and determine how much weight any single result can bear.

Small samples. Most human neuroimaging studies of love and rejection have enrolled roughly ten to thirty participants. Low statistical power reduces the chance of detecting true effects and also increases the probability that a significant result is a false positive and inflates the effect sizes that are detected (Button et al., 2013).

Reverse inference. Imaging studies frequently reason backward from activation in a region to the presence of a mental process: because the ventral striatum is active during reward, its activation during exposure to an ex-partner's photograph is taken to show "craving." This inference is valid only to the degree that the region is selectively engaged by that process, and most regions are engaged by many processes (Poldrack, 2006). The same caution applies to the anterior cingulate cortex and "pain" (Section 4.4).

Peripheral measures of central chemistry. Blood, saliva and platelet measures are often used as proxies for brain neurochemistry. For oxytocin the proxy is poor and widely used assays are unreliable (Section 3.3); for serotonin, peripheral measures are at best indirect.

Animal-to-human translation. Much mechanistic evidence comes from the socially monogamous prairie vole (*Microtus ochrogaster*). Vole studies permit experiments impossible in humans, but a rodent pair bond is not a validated model of human romantic love, and some foundational vole findings have been revised (Section 3.3).

Sample composition. Participants are overwhelmingly young adults from Western, educated, industrialized, rich and democratic (WEIRD) societies, a population unrepresentative of humanity on many psychological measures (Henrich et al., 2010). Most studies recruit heterosexual participants, many recruit only women or students, and few report on gender-diverse participants. Generalizations beyond these groups are untested rather than disconfirmed.

3. The neurobiology of romantic attachment

3.1 Dopamine, wanting and liking

A frequently repeated statement holds that dopamine produces not pleasure but the urge to seek more. This is a fair compression of a substantial literature. Berridge and Robinson distinguish *wanting* (incentive salience: the motivational pull of a reward and its cues) from *liking* (the hedonic impact of the reward itself). Mesolimbic dopamine is closely tied to wanting and comparatively little to liking, and repeated drug use can sensitize wanting so that cues trigger strong urges even when the drug is no longer much enjoyed (Berridge & Robinson, 2016). Dopamine neurons also signal *reward prediction errors*, differences between expected and received outcomes that drive learning about what to pursue, a mechanism that has been applied to grief (O'Connor & Seeley, 2022).

A partner is a highly salient, repeatedly encountered source of reward with many associated cues: a face, a voice, places, routines. Wanting-like states, prediction errors when expected contact does not arrive, and cue-triggered urges are therefore plausible components of the response to loss. That plausibility rests on general principles of learning and motivation, not on measurements in heartbroken people: no published study known to the Institute has measured dopamine release in humans after a breakup.

Evidence strength: the role of dopamine in incentive salience and learning is **Established** in general; its application to romantic loss is **Supported** as a framework and **Preliminary** as a direct finding.

3.2 Neuroimaging of romantic love

In a widely cited fMRI study, participants in the early stage of intense romantic love viewed photographs of their beloved and of a familiar acquaintance. Viewing the beloved was associated with activation in the right VTA and caudate nucleus, regions associated with reward and motivation, and the authors proposed that romantic love is better understood as a goal-directed motivational state than as a specific emotion (Aron et al., 2005). That proposal is the most defensible part of the neurochemical account of love: it locates love among motivational systems without claiming that a single chemical constitutes it.

Three limits apply. BOLD activation in a dopamine-rich region does not show that dopamine was released. The studies used small, highly selected samples and a single paradigm (passive photograph viewing), limiting ecological validity. And reward regions respond to many salient stimuli, from familiar faces to money and food, so activation alone does not distinguish love from other salient experiences. Evidence strength: engagement of reward-related regions by images of a partner is **Supported**; the claim that early love increases dopamine release in the human nucleus accumbens and VTA, stated as a measured fact, is **Preliminary**.

3.3 Oxytocin and vasopressin

It is often said that oxytocin strengthens trust and pair bonding and that vasopressin increases attachment and protective behavior, together creating a neurological sense of safety. The animal and human evidence for this claim should be assessed separately.

Animal evidence. In prairie voles, pharmacological studies over three decades indicated that oxytocin and vasopressin signaling in reward-related regions is required for partner preferences to form, and these findings motivated influential syntheses linking attachment, love and addiction (Burkett & Young, 2012). Using CRISPR gene editing, however, Berendzen et al. (2023) produced prairie voles lacking a functional oxytocin receptor that still formed partner preferences, gave birth and cared for their young. Developmental compensation may be involved, but oxytocin receptor signaling is evidently not strictly necessary for pair bonding even in the species on which the theory was built.

Human evidence. Human research has relied on two methods, both seriously problematic. The first is peripheral measurement in blood or saliva. A pre-registered meta-analysis of 17 studies (516

participants and subjects) found no significant association between central and peripheral oxytocin under basal conditions ($r = 0.08$, under 1% shared variance), although associations emerged after intranasal administration and experimentally induced stress (Valstad et al., 2017). Commercial immunoassays used on unextracted samples are unreliable and detect molecules other than oxytocin (McCullough et al., 2013). Findings such as higher plasma oxytocin in new lovers than in single people (Schneiderman et al., 2012) are therefore difficult to interpret as evidence about brain oxytocin.

The second method is intranasal administration. Very little intranasal oxytocin appears to reach the cerebrospinal fluid, while blood levels rise to supraphysiological concentrations, so behavioral effects cannot be confidently attributed to central action (Leng & Ludwig, 2016). The best-known behavioral finding, that intranasal oxytocin increases trust in an economic game, has replicated poorly (Nave et al., 2015), and a pre-registered replication with power above 95% found no effect in the condition that mirrored the original study (Declerck et al., 2020).

Evidence strength: a contribution of oxytocin and vasopressin to bonding in some mammals is **Supported**, with redundancy shown by knockout studies. That oxytocin produces trust, safety or bonding in humans is **Contested**. A breakup-induced "oxytocin collapse" causing loneliness, panic and sleep disturbance is **Speculative**: no study has measured central oxytocin before and after human romantic loss, and peripheral measures could not answer the question.

3.4 Serotonin and obsessive thinking

A related claim holds that early romantic obsession reduces serotonin, producing intrusive thoughts and idealization that mirror obsessive-compulsive disorder (OCD). The claim traces to a study of 20 people recently in love, 20 unmedicated patients with OCD and 20 controls, in which both the in-love and OCD groups showed lower serotonin transporter binding on blood platelets than controls (Marazziti et al., 1999). A later study of 20 people in love and 20 not in love, half of each group men, found lower blood serotonin in men in love but the opposite pattern in women (Langeslag et al., 2012). Its participants reported thinking about their beloved for about 65% of their waking hours, a vivid confirmation of the phenomenon if not of its mechanism.

The serotonin claim therefore rests on two small studies with peripheral measures and inconsistent results, the second showing effects in opposite directions by sex. Evidence strength: intrusive, preoccupying thought in early love is **Supported** by self-report; its causation by reduced serotonin is **Preliminary to Contested**; a neurochemical equivalence with OCD is **Speculative**.

3.5 Stress hormones in early love

Romantic attachment is not neurochemically "safe" from its beginning. Comparing 24 people recently in love with 24 who were not, Marazziti and Canale (2004) found higher cortisol in the in-love group, lower testosterone in men in love and higher testosterone in women in love, with all differences gone 12 to 24 months later. Early love may itself be an arousing, somewhat stressful state, which sits poorly with a narrative in which love supplies calm and loss removes it. Evidence strength: **Preliminary**.

3.6 Endogenous opioids

The *brain opioid theory of social attachment* proposes that endogenous opioids contribute to the comfort of social contact and that their withdrawal contributes to separation distress. Human evidence is limited but includes receptor-level measurement. In a PET study of 18 participants, social rejection in a simulated social-feedback task reduced μ -opioid receptor availability, consistent with endogenous opioid release, in the ventral striatum, amygdala, midline thalamus and periaqueductal gray, and greater release in some regions correlated with trait resilience (Hsu et al., 2013). Rejection was thus associated with *increased* opioid activity, interpreted as buffering, not with an "endorphin deficiency." The common claim that heartbreak depletes the body's natural pain relief is not supported by the most direct human evidence. Evidence strength: opioid involvement in responses to rejection is **Preliminary**; the deficiency claim is **Speculative** and in tension with the data.

4. What happens in the body and brain after romantic loss

4.1 Neuroimaging of rejection and breakup grief

Three small fMRI studies form the empirical core of the neural account of heartbreak. Fisher et al. (2010) scanned 15 people (10 women, 5 men) recently rejected by a partner they still loved intensely. Viewing the rejecting partner, compared with a familiar person, activated the VTA, ventral striatum, orbitofrontal and prefrontal cortex, and cingulate gyrus; the authors noted that several of these regions had been associated with cocaine craving and proposed that the overlap may help explain obsessive behavior after rejection.

Najib et al. (2004) scanned nine women whose relationships had ended within four months while they alternated between a sad, ruminative thought about the former partner and a neutral thought. Acute grief was associated with increased activity in posterior regions, including the cerebellum, and *decreased* activity in anterior regions including the striatum, insula, and anterior cingulate and prefrontal cortex; women reporting more recent grief showed larger decreases.

In bereavement, reminders of the deceased elicited pain-related activity in women with both complicated ($n = 11$) and noncomplicated ($n = 12$) grief, but nucleus accumbens activity only in those with complicated grief, correlated with self-reported yearning (O'Connor et al., 2008).

Reminders of a lost partner therefore engage reward, emotion and regulatory regions, and persistent reward-related responses may characterize people who are not adapting. But the studies are small, use different contrasts and disagree in detail: one reports striatal increases, another striatal decreases. A meta-analysis of studies of reliving a romantic rejection found activation both within and beyond the network seen in laboratory social-exclusion tasks (Cacioppo et al., 2013). Evidence strength: regional engagement by reminders of a lost partner is **Supported**; any particular neural signature of heartbreak is **Preliminary**.

4.2 Stress physiology after separation

The claim that cortisol rises sharply and stays elevated for long periods after heartbreak is a natural extrapolation from stress research, but the specific evidence is thin. A meta-analysis of 208 laboratory studies found that stressors combining uncontrollability with social-evaluative threat, in which a person's competence or worth could be judged by others, produced the largest cortisol responses and slowest recovery (Dickerson & Kemeny, 2004). Romantic rejection plausibly carries both features, which makes HPA activation a reasonable prediction.

Direct human evidence comes mostly from temporary separations. In a 21-day diary study of 42 couples spanning a work-related separation of four to seven days, separation was associated with changes in affect, sleep problems, subjective stress, physical symptoms and cortisol, more strongly for partners high in attachment anxiety and those with less contact during the separation (Diamond et al., 2008). In prairie voles, males separated from a female partner, but not from a male sibling, showed increased passive stress-coping and elevated corticosterone, and blocking corticotropin-releasing factor receptors prevented the behavioral change without disrupting the bond (Bosch et al., 2009). This is among the clearest experimental evidence linking partner loss to stress systems, but it is rodent evidence.

Sbarra and Hazan (2008) synthesized this literature into a *coregulation* model: in an established relationship, partners' physiology becomes partly interwoven, so that each partner helps regulate the other's arousal; separation removes this regulation and can produce states ranging from diffuse arousal to a full stress response; recovery requires a shift to self-regulation. The model is close in spirit to the weak withdrawal hypothesis but replaces the metaphor of a drug supply with the better specified idea of lost regulatory support, and it predicts who will show the largest disruption.

Evidence strength: that relationship loss can activate stress physiology is **Supported**. Reliable, persistent cortisol elevation after human breakups is **Preliminary**: longitudinal studies with standardized repeated sampling from the time of a breakup are rare, and cortisol varies with time of day, sleep, medication and other factors. Downstream effects often attributed to a "cortisol spike" (inflammation, suppressed immunity, digestive problems) are plausible consequences of chronic stress in general but untested in breakup samples.

4.3 Stress cardiomyopathy: the literal "broken heart"

One part of the heartbreak vocabulary refers to a real medical condition. *Takotsubo syndrome*, also called stress cardiomyopathy or "broken-heart syndrome," is an acute, usually reversible weakening of the left ventricle that mimics a heart attack.

The International Takotsubo Registry included 1,750 patients from 26 hospital centers in Europe and the United States; 89.8% were women, with a mean age of 66.8 years. Emotional triggers were less common than physical triggers (27.7% vs 36.0%), and 28.5% had no evident trigger, leaving 7.8% in other trigger categories. Compared with matched patients with acute coronary syndrome, patients had more neurologic or psychiatric disorders and similar rates of severe in-hospital complications,

including shock and death; during follow-up the death rate was 5.6% per patient-year (Templin et al., 2015). An international expert consensus describes the condition as underrecognized, potentially severe and probably more prevalent than estimated (Ghadri et al., 2018).

Three points matter. Takotsubo is uncommon and predominantly affects older, postmenopausal women, not the young adults who dominate the heartbreak literature. Emotional triggers in registries include many kinds of acute distress, and published summaries generally do not isolate breakups. And because physical triggers are more common and over a quarter of patients have no identified trigger, the image of a heart broken by sorrow describes a minority of cases.

A related association concerns bereavement. In a UK primary-care cohort of 30,447 people aged 60 to 89 whose partner died, 50 (0.16%) had a heart attack or stroke within 30 days, compared with 67 of 83,588 matched controls (0.08%), an adjusted incidence rate ratio of 2.20 (95% CI 1.52 to 3.15) that attenuated after 30 days (Carey et al., 2014). Relative risk roughly doubled, but the absolute excess was about 8 events per 10,000 bereaved people in the first month, and the finding concerns the death of a long-term partner among older adults, not breakups.

Evidence strength: that acute emotional stress can trigger takotsubo syndrome is **Established**; a short-term rise in cardiovascular events after partner bereavement in older adults is **Supported**; clinically meaningful cardiac risk from breakups in young adults is **Speculative**. Chest pain or breathlessness after a distressing event should be treated as a medical emergency, not as heartbreak.

4.4 Is rejection "pain"? The social-pain overlap debate

A common claim holds that heartbreak activates the dorsal anterior cingulate cortex (dACC), described as the same region that processes physical pain, and that this explains its visceral quality. This is the most actively contested question reviewed here.

The case for overlap. In an early fMRI study using Cyberball, a virtual ball-tossing game in which participants are excluded by other players, exclusion increased dACC activity, which correlated with self-reported distress (Eisenberger et al., 2003). Kross et al. (2011) had people who had recently experienced an unwanted breakup view a photograph of their former partner while thinking about the rejection and, separately, receive painful heat. Both conditions activated secondary somatosensory cortex and dorsal posterior insula, regions associated with the sensory components of pain. Using a large database of published studies, Lieberman and Eisenberger (2015) argued that reverse inference from dACC activity points more strongly to pain than to executive control, conflict or salience.

The case against identity. Using a similar paradigm with 60 participants, Woo et al. (2014) trained multivariate pattern classifiers on fMRI data. In new individuals, a pain classifier distinguished painful from warm stimulation with 92% accuracy and a rejection classifier distinguished ex-partner from friend photographs with 80% accuracy, yet each performed at chance on the other condition, and the two patterns were uncorrelated even within dACC. A meta-analysis of Cyberball studies with 244 participants likewise failed to support the claim that rejection engages the same "pain matrix" as nociceptive stimuli (Cacioppo et al., 2013). Iannetti et al. (2013) argued that much activity attributed

to a pain matrix reflects detection of salient events in any modality, so overlap does not demonstrate a shared mechanism, and a group of pain and imaging researchers disputed the large-scale reverse-inference analysis on the grounds that the dACC is engaged by many processes (Wager et al., 2016).

Verdict. Rejection and physical pain are both aversive, can both produce bodily sensations, and engage some overlapping regions at conventional fMRI resolution. The claims that rejection uses the "same circuits" as pain or that dACC activation "explains" heartbreak are not supported by the multivariate evidence. Evidence strength: regional overlap is **Supported**; shared neural representation is **Contested**, with the better powered evidence favoring distinct representations.

5. Evaluating the withdrawal hypothesis

5.1 The best case for the hypothesis

The strongest version of the argument runs as follows. Romantic attachment engages mesolimbic reward circuitry (Aron et al., 2005). Reminders of a rejecting partner engage regions also engaged in drug craving (Fisher et al., 2010). In animals, the neurochemical systems implicated in pair bonding (dopamine, opioids, corticotropin-releasing factor, and the neuropeptides oxytocin and vasopressin) overlap substantially with those implicated in addiction (Burkett & Young, 2012), and partner loss in voles produces a stress-system-dependent behavioral change reminiscent of withdrawal (Bosch et al., 2009). Addiction research has described a "dark side" of reward in which repeated drug use recruits stress systems, so that withdrawal is marked by negative affect driven partly by stress neurochemistry (Koob & Le Moal, 2001). At the behavioral level, rejected lovers often report craving-like yearning, cue-triggered intrusions, compulsive checking, and relapse-like contact with the former partner. In bereavement, persistent reward-related responses to reminders appear to distinguish complicated from noncomplicated grief (O'Connor et al., 2008). The analogy therefore organizes a set of otherwise scattered findings and generates testable predictions.

5.2 The principal objections

The analogy depends on a contested model of addiction. The withdrawal framing borrows from the brain disease model, which describes addiction as a chronic condition produced by drug-induced changes in reward, stress and executive circuits (Volkow et al., 2016). Lewis (2018) argued that the same brain changes are better understood as an extreme form of normal learning and habit formation that accompanies any intensely pursued goal. On that view, the similarity between love and addiction says as much about ordinary learning as about pathology. Either way, the analogy cannot carry the implication that heartbreak is a disease.

"Addicted to love" is a conceptual choice, not a discovery. Earp et al. (2017) distinguished a narrow view, on which only abnormal, harmful attachments count as addiction, from a broad view, on which all romantic love involves addiction-like processes on a continuum. On the broad view, calling heartbreak withdrawal merely redescribes normal attachment; on the narrow view, it applies only to a

minority of harmful cases. Imaging data cannot settle the choice, which carries the ethical risk of pathologizing ordinary grief.

No neurochemical deficit has been measured. The strong form of the hypothesis is a claim about neurochemical supply and deficit. Human studies have measured BOLD signals, peripheral hormones and, in one PET study, opioid receptor availability during simulated rejection, but none has measured dopamine, oxytocin or serotonin in the brain before and after a real breakup. Where the most direct evidence exists, for the opioid system, its direction runs against the deficiency narrative (Hsu et al., 2013).

Reverse inference. Moving from "regions active during craving are active when viewing an ex-partner" to "rejected people crave their ex-partner as addicts crave drugs" requires regional selectivity that the ventral striatum, VTA and orbitofrontal cortex, engaged by a wide range of salient stimuli, do not have (Poldrack, 2006).

A learning account explains the same data with fewer assumptions. O'Connor and Seeley (2022) propose that grieving is a form of learning: semantic knowledge that an attachment figure is permanently available conflicts with episodic knowledge of the loss, and resolving that conflict requires time and experiential feedback. Applied to breakups, this account predicts craving-like yearning, cue-triggered intrusions and a gradual decline as expectations are updated, without positing a chemical dependency. It also locates risk in factors that impede learning, such as avoidance and rumination, which are modifiable and well studied (Section 6).

Biological descriptions are not causes of experience. Even where a neurochemical change accompanies distress, it is one level of description of an event that also has psychological, relational and social levels (IHE-WP-01). Phrasing in which a chemical creates loneliness or panic treats a correlate as the cause and ignores the reverse direction of influence: appraisals, memories, social context and behavior shape neurochemistry as much as neurochemistry shapes them.

5.3 Verdict and reformulation

The strong form of the withdrawal hypothesis, in which heartbreak is pharmacological withdrawal caused by neurochemical deficits, is **Speculative** and in places contradicted by the evidence. The weak form, in which romantic loss engages motivational, stress-regulatory and learning systems that also figure in addiction, is **Supported** as a framework and useful for generating hypotheses, provided it is not read as a diagnosis.

A more defensible formulation, consistent with Sbarra and Hazan (2008) and O'Connor and Seeley (2022), is that romantic loss combines three processes: (a) loss of *coregulation*, the external regulation of arousal and emotion provided by a partner; (b) violated reward predictions and persistent incentive salience of partner-related cues, which decline as expectations are updated; and (c) disruption of a self-concept partly built around the relationship. Each process has biological, psychological and social aspects, and each is open to measurement. Describing heartbreak as an "injury" adds rhetorical force but no explanatory content and should be avoided.

6. Psychological processes and heterogeneity of recovery

The neurochemical framing tends to imply a uniform trajectory: a crash, a loop, and a long road back that requires intervention. The longitudinal psychological literature describes something different.

6.1 Most people recover

Research on bereavement and potentially traumatic events shows that *resilience*, relatively stable functioning with only transient disruption, is a common response to loss, distinct from a trajectory of initial distress followed by gradual recovery, more common than clinicians long assumed, and reached through multiple pathways (Bonanno, 2004). Breakup research is broadly consistent. In a daily-diary study of young adults after a nonmarital breakup, distress declined on average over the following weeks, with considerable day-to-day fluctuation (Sbarra & Emery, 2005), and people tend to overpredict how distressed a breakup will make them (Eastwick et al., 2008).

Breakups are nonetheless consequential. In a national sample of 1,295 unmarried 18- to 35-year-olds followed for 20 months, 36.5% experienced at least one breakup, which was associated with increased distress and reduced life satisfaction; declines in life satisfaction were larger after cohabitation or marriage plans and smaller for those who had begun dating someone new (Rhoades et al., 2011). Distress after a breakup is real, common and usually temporary, and its size depends on the relationship, the person and their circumstances.

Evidence strength: that most people recover from breakups without professional intervention is **Supported**; that resilience is a common response to loss in general is **Established**.

6.2 Grief, depression and risk

Grief after a breakup and major depression share symptoms but are not the same. In the US National Comorbidity Survey, uncomplicated depressive episodes triggered by losses other than bereavement, including relationship loss, resembled uncomplicated bereavement-triggered episodes on eight of nine indicators of disorder, and both differed markedly from complicated reactions (Wakefield et al., 2007). This supports treating short-lived, proportionate distress after a breakup as a normal reaction while recognizing that some reactions warrant clinical attention.

For a minority, a breakup is a genuine risk factor. In a prospective study of adolescents, a recent romantic breakup predicted first onset of major depressive disorder (Monroe et al., 1999). Among 71 adults with a breakup in the past six months, compared with 46 in a relationship, depression scores were elevated on average, and 26.8% (about 19 people) reported mild, moderate or severe depressive symptoms (Verhallen et al., 2019). Education should therefore help people recognize when ordinary grief has become something more (Section 8.3).

6.3 Self-concept

Relationships change the people in them. In prospective studies, falling in love was followed by increased diversity of self-concept content, consistent with partners incorporating aspects of each other

into the self (Aron et al., 1995). When the relationship ends, that integration becomes a vulnerability. Across three studies, breakups were followed by changes in self-concept content and reduced *self-concept clarity*, the extent to which beliefs about oneself are clear, consistent and stable, and reduced clarity uniquely predicted distress (Slotter et al., 2010). Simply participating in a measurement-intensive study of breakup recovery, with repeated reflective assessments over nine weeks, was associated with larger decreases in self-concept disturbance than minimal assessment, and improved clarity accounted for decreases in emotional intrusion and loneliness (Larson & Sbarra, 2015).

The claim that heartbreak disrupts identity is thus one of the better supported claims in popular accounts, but the evidence is psychological rather than neurochemical. Evidence strength: **Supported**.

6.4 Rumination, contact and monitoring

Rumination, repetitive and passive focus on one's distress and its causes and consequences, prolongs negative mood and predicts the onset of depression across many contexts (Nolen-Hoeksema et al., 2008). The "feedback loop" of popular accounts, in which reminders trigger craving, checking and renewed distress, is better described in these well-studied psychological terms than as a sequence of chemical drops.

Behavior that maintains exposure to the former partner may amplify the loop. In a cross-sectional survey of 464 people, monitoring a former partner's social media profile was associated with greater distress, more longing and lower personal growth, controlling for offline contact (Marshall, 2012); the direction of influence is unknown, since people who are struggling may monitor more. Among people distressed by a breakup, negative reappraisal of the former partner reduced love feelings but worsened mood, whereas distraction improved mood without changing love feelings, and all strategies reduced an electrophysiological marker of motivated attention to the former partner (Langeslag & Sanchez, 2018).

Evidence strength: rumination as a general risk factor for prolonged distress is **Established**; the specific harms of post-breakup monitoring are **Preliminary**, given cross-sectional data.

6.5 Attachment

Adult romantic love has been conceptualized as an attachment process, analogous in some respects to the infant-caregiver bond, with individual differences in security, anxiety and avoidance (Hazan & Shaver, 1987). In an online survey of more than 5,000 respondents, attachment anxiety was associated with greater preoccupation with the lost partner, more intense distress, more attempts to reestablish the relationship and more use of alcohol and drugs to cope; avoidance was associated with self-reliant coping, and security with turning to friends and family (Davis et al., 2003). Anxiety also amplifies responses to temporary separation (Diamond et al., 2008), making it one of the more important moderators of loss. Self-selected samples limit generalization, and attachment orientations are only moderately stable (IHE-WP-01), so they are tendencies, not fixed types.

7. Sex, gender and diversity

It is commonly claimed that men experience a distinctive, delayed "crash" in which testosterone masks vulnerability until dopamine collapses, that men suppress oxytocin processing, and that men's smaller support networks prolong recovery.

There is no direct evidence for a testosterone-masking mechanism or for sex differences in post-breakup dopamine or oxytocin dynamics, and the best hormonal evidence cuts against a simple account. Among 258 heterosexual and non-heterosexual women and men, partnered people had lower testosterone among heterosexual men and non-heterosexual women but not among heterosexual women or non-heterosexual men; longitudinally, changes in partnership status did not change testosterone, and lower baseline testosterone predicted later partnering (van Anders & Watson, 2006). Testosterone-relationship associations thus appear trait-like and dependent on partner orientation rather than sex alone.

Self-report data on sex differences are mixed. In a large international online survey, women reported more intense emotional and physical pain after a breakup than men (Morris et al., 2015). In a diverse community sample of young adults, recent breakups were more closely associated with women's mental health, whereas support and strain in ongoing relationships were more closely associated with men's (Simon & Barrett, 2010). Gender norms about expressing distress and seeking help plausibly shape these patterns, and differences in how distress is expressed (depressed mood versus substance use, for example) complicate comparisons. That men typically feel the full weight of a breakup only weeks or months later has not been tested prospectively in studies known to the Institute and is **Speculative**.

Sexual and gender diversity is a major gap. Most imaging and hormonal studies recruit heterosexual participants, and almost none report on transgender or nonbinary participants. There is no principled reason to expect coregulation, prediction error or self-concept change to differ by orientation, but sexual minority individuals may face distinctive stressors after a breakup, such as smaller partner pools in some settings, overlapping friendship networks and less social recognition of their relationships; these are research questions, not findings. Almost all of the evidence comes from WEIRD samples (Henrich et al., 2010), and cultural variation in norms around relationships and separation is largely unexamined.

8. Implications for preventive education

The evidence does not support any "neurochemical" intervention for heartbreak. There is no validated way to measure a heartbroken person's neurochemical state, no evidence known to the Institute that breathing techniques alter stress hormones enough to affect breakup recovery, and no basis for drug, supplement or hormone use for this purpose. The evidence does identify modifiable psychological and behavioral factors associated with recovery that education can address. IHE provides preventive

education: it does not provide treatment or diagnose, and it refers people who need clinical care to licensed clinicians.

8.1 What the evidence suggests for education

The following themes are candidates for preventive psychoeducation. Each is supported by correlational or experimental evidence of varying strength, as indicated, and none has been tested as an IHE program.

- **Normalizing without pathologizing.** Distress after a breakup is common and usually declines over weeks to months (Sbarra & Emery, 2005; Rhoades et al., 2011), and people tend to overestimate it in advance (Eastwick et al., 2008). The withdrawal metaphor may help some people make sense of craving-like yearning, but presenting heartbreak as a brain injury implies a need for specialist intervention that the evidence does not support.
- **Rebuilding self-concept clarity.** Reduced self-concept clarity predicts post-breakup distress (Slotter et al., 2010), and structured reflection may help (Larson & Sbarra, 2015). Educational content can encourage people to reconnect with activities, relationships and goals that are not tied to the former partner.
- **Recognizing rumination.** Distinguishing reflective problem-solving from passive, repetitive brooding, and learning to interrupt the latter, is grounded in a large literature (Nolen-Hoeksema et al., 2008).
- **Managing exposure to reminders.** Reducing monitoring of a former partner may be helpful for some people (Marshall, 2012), with the caution that the evidence is correlational and that complete avoidance can interfere with the learning that grief requires (O'Connor & Seeley, 2022).
- **Choosing regulation strategies deliberately.** Reappraisal and distraction have different effects on love feelings and mood (Langeslag & Sanchez, 2018); education can present them as tools with trade-offs rather than as a single correct method.
- **Sleep.** Sleep disturbance is common during separation (Diamond et al., 2008), and sleep has wide-ranging effects on immune and emotional functioning (Irwin, 2015). Basic sleep hygiene is a low-risk educational topic, although its specific effect on breakup recovery has not been tested.
- **Social connection.** Across 148 studies with 308,849 participants, stronger social relationships were associated with higher odds of survival (Holt-Lunstad et al., 2010), and securely attached people tend to turn to friends and family after a breakup (Davis et al., 2003). Encouraging people, especially those whose social lives were organized around the relationship, to maintain and rebuild support networks is consistent with this evidence.

8.2 A caution about well-intended techniques

Interventions that seem obviously helpful can cause harm. In a randomized study of 90 adults after marital separation, those actively searching for meaning in the separation reported worse emotional outcomes up to nine months later when assigned to expressive writing about it than when assigned to control writing (Sbarra et al., 2013). Educational content should be evaluated, ideally in pre-registered trials that monitor harms, before it is promoted, and techniques without an evidence base should not be offered.

8.3 When to seek clinical care

Education is not a substitute for professional help. In general terms, a person should seek care from a licensed clinician, such as a primary care physician, psychologist or psychiatrist, if after a breakup they experience:

- depressed mood or loss of interest or pleasure most of the day, nearly every day, for two weeks or more, or distress that is not easing after several months;
- thoughts of self-harm or suicide, which call for immediate help (in the United States, the 988 Suicide and Crisis Lifeline can be reached by call or text; elsewhere, local emergency services);
- substantial difficulty functioning at work, school or in caring for themselves or others;
- reliance on alcohol or other drugs to cope;
- chest pain, breathlessness or fainting, which should be treated as a medical emergency;
- urges to harm, threaten or pursue a former partner, or experiences of being threatened, stalked or harmed by one.

9. Ethical considerations

Pathologizing normal experience. Describing heartbreak as an injury, disease or addiction can make ordinary grief seem abnormal and encourage people to seek, or be sold, unnecessary interventions. Accurate framing respects both the seriousness of loss and people's capacity to recover.

Biological determinism and responsibility. Neurochemical language can be used to excuse harmful behavior ("my brain was in withdrawal") or to cast people as passive recipients of chemical states; the evidence supports neither. Persistent contact attempts, monitoring and pursuit of a former partner against their wishes are matters of consent and safety.

Misuse for manipulation. Knowledge that intermittent reward, uncertainty and cue exposure can intensify attachment could in principle be used to cultivate dependence in a partner or to exploit someone's vulnerability after a breakup. Such uses fall outside the definition of seduction used in this series and are incompatible with IHE's commitments to consent, autonomy and dignity.

Commercial exploitation. The prestige of neuroscience makes neurochemical claims effective marketing. Products and services promising to "reset" brain chemistry after a breakup are not supported by the evidence reviewed here. IHE has no products and makes no such claims.

Privacy of relationship and biometric data. Heartbreak research involves intimate information about participants and about former partners who have not consented to be studied. Physiological, neuroimaging and digital-trace data are sensitive and require ethical review, minimization of third-party data, secure storage, and explicit consent for secondary use.

Research with distressed participants. People recruited soon after a breakup may be vulnerable. Studies should screen for risk, provide referral information and monitor for harm, since participation itself can change outcomes for better (Larson & Sbarra, 2015) or worse (Sbarra et al., 2013).

Cultural sensitivity. Norms about romantic relationships, separation and grief differ across cultures, religions and communities. Educational content built on WEIRD samples should not be presented as universal.

10. Evidence at a glance

Table 1. Central claims of this paper, with evidence strength and principal limitations.

Claim	Evidence strength	Representative sources	Principal limitation
Images of a romantic partner engage reward-related regions	Supported	(Aron et al., 2005; Fisher et al., 2010)	Small samples; BOLD is not dopamine
Dopamine is linked to wanting rather than liking	Established	(Berridge & Robinson, 2016)	Mainly animal and drug research
Oxytocin is necessary for pair bonding	Contested	(Burkett & Young, 2012; Berendzen et al., 2023)	Vole evidence; redundancy in knockouts
Peripheral oxytocin indexes brain oxytocin	Contested	(Valstad et al., 2017; McCullough et al., 2013)	No basal association; assay problems
Intranasal oxytocin increases trust	Contested	(Nave et al., 2015; Declerck et al., 2020)	Failed preregistered replication
Reduced serotonin underlies love's obsessive thinking	Preliminary to Contested	(Marazziti et al., 1999; Langeslag et al., 2012)	Two small peripheral studies
Separation disrupts stress physiology	Supported	(Diamond et al., 2008; Bosch et al., 2009; Sbarra & Hazan, 2008)	Few human breakup studies
Rejection engages opioid release	Preliminary	(Hsu et al., 2013)	One PET study, n = 18
Rejection and physical pain share neural representations	Contested	(Kross et al., 2011; Woo et al., 2014; Cacioppo et al., 2013)	Reverse inference; classifier evidence

Claim	Evidence strength	Representative sources	Principal limitation
Emotional stress can trigger takotsubo syndrome	Established	(Templin et al., 2015; Ghadri et al., 2018)	Mostly older women; breakups rarely isolated
Partner bereavement raises short-term cardiovascular risk	Supported	(Carey et al., 2014)	Older adults; death, not breakup
Heartbreak is pharmacological withdrawal	Speculative	(Earp et al., 2017; Lewis, 2018)	No neurochemical deficit measured
Most people recover from breakups without treatment	Supported	(Bonanno, 2004; Sbarra & Emery, 2005; Rhoades et al., 2011)	Young, Western samples
Lower self-concept clarity predicts post-breakup distress	Supported	(Slotter et al., 2010; Larson & Sbarra, 2015)	Mostly student samples
Attachment anxiety amplifies breakup distress	Supported	(Davis et al., 2003; Diamond et al., 2008)	Self-selected and self-report data
Men show a testosterone-masked delayed crash	Speculative	(van Anders & Watson, 2006)	No direct evidence

11. Limitations and open questions

This paper is a narrative review, not a systematic review: sources were selected to represent the principal findings and critiques in each area, without a formal search protocol or risk-of-bias assessment, and its evidence grades are considered judgments open to revision.

The evidence base has structural weaknesses. Human neuroimaging of romantic loss rests on a handful of small studies with heterogeneous paradigms, and no large, pre-registered study exists. Human neurochemical claims rest mostly on peripheral measures or BOLD inference, and experimental manipulation is largely confined to rodents. Longitudinal physiological studies from the time of a breakup are rare; most psychological studies rely on self-report from convenience samples. Publication bias is likely throughout. Breakups are not randomly assigned, so associations with outcomes are vulnerable to confounding by personality, relationship history and circumstance.

Open questions include: Does cue reactivity in reward-related regions decline after a breakup, and does its rate of decline predict recovery? Is persistent reward-related reactivity a marker of complicated reactions, as in bereavement (O'Connor et al., 2008)? Which components of the coregulation model can be measured reliably outside the laboratory? How do responses differ by age, culture, sexual orientation, gender identity and relationship form, and between being rejected, ending a relationship oneself and mutual dissolution? How much of the apparent sex difference reflects how distress is expressed and measured?

12. Research agenda

The following questions are aspirations for a young institute working with university partners under IRB supervision and review by IHE's Independent Ethics Committee. None has been conducted. Each is designed for pre-registration of hypotheses, primary outcomes and analysis plans, with null results reported.

1. **Prospective test of cue-reactivity decline.** In an adequately powered longitudinal fMRI study of recently separated adults, the weak withdrawal hypothesis predicts that ventral striatal responses to partner cues will decline over months and that slower decline will predict greater yearning and distress. The prediction is falsified if reactivity does not decline, or if its trajectory is unrelated to distress once self-reported love for the former partner is controlled.
2. **Specificity of rejection representations.** Replicating and extending the multivariate approach of Woo et al. (2014) in a new sample would test whether rejection-related patterns are distinct from pain-related patterns and whether they predict distress beyond self-report.
3. **Coregulation and stress physiology.** Ambulatory studies with standardized cortisol sampling (waking response, diurnal slope) and sleep measurement, beginning soon after a breakup, would test whether attachment anxiety and loss of daily contact predict larger and longer disruptions (Sbarra & Hazan, 2008; Diamond et al., 2008).
4. **Brief educational module with harm monitoring.** A randomized trial could compare a short preventive-education module (accurate expectations, self-concept rebuilding, rumination awareness, sleep, social connection) with an active control, with pre-registered outcomes for distress and self-concept clarity and explicit monitoring of adverse effects (Sbarra et al., 2013). A null result would count against adopting the module.
5. **Diversity and generalization.** Studies including same-sex and gender-diverse couples, older adults, and non-WEIRD samples would test whether the processes reviewed here generalize, rather than assuming that they do.
6. **Modeling recovery trajectories.** Using the modeling framework of IHE-WP-05, survival and growth-mixture models could estimate the proportions of people following resilient, recovering and chronic trajectories after breakups, with population-level rather than individual-level aims.
7. **Olfactory reminders.** IHE-WP-04 discusses the hypothesis that scent acts as a potent emotional cue. Whether olfactory reminders of a former partner elicit stronger or longer-lasting cue reactivity than visual reminders is **Speculative** and experimentally testable.

Why romantic loss should be so distressing, including the hypothesis that separation distress motivates proximity seeking (Bosch et al., 2009), and the limits of such adaptationist explanations, are taken up in IHE-WP-03.

13. Conclusion

The intuition behind the claim that heartbreak is withdrawal is not baseless. Romantic attachment engages systems of motivation and learning that are also central to addiction, reminders of a lost partner engage reward-related brain regions, separation can disrupt stress physiology, and in rare cases intense emotional stress can injure the heart. These findings justify taking the biology of heartbreak seriously.

They do not justify the stronger claims made on their behalf. No study has shown that a breakup depletes dopamine, oxytocin, serotonin or endorphins in the human brain; the oxytocin literature is beset by measurement problems and failed replications; the overlap between social and physical pain is contested; and the neuroimaging evidence comes from small samples interpreted through reverse inference. The best evidence about recovery is psychological: most people recover, and self-concept clarity, rumination, attachment anxiety, social connection and exposure to reminders are better studied correlates of recovery than any chemical marker.

A calibrated account therefore treats heartbreak as a biopsychosocial response to the loss of a regulatory, rewarding and identity-defining relationship. It is real, often painful, usually temporary, occasionally the beginning of a clinical problem, and best addressed through accurate understanding, social support and, where needed, professional care.

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