Journal of Affective Disorders 317 (2022) 98–106

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Treatment of adjustment disorder stemming from romantic betrayal using memory reactivation under propranolol: A open-label interrupted time series trial☆

Michelle Lonergan [a,b], Daniel Saumier [b,c], Sereena Pigeon [b,d], Pierre E. Etienne [b], Alain Brunet [b,e,*]

[a] University of Ottawa, School of Psychology, Ottawa, Ontario, Canada
[b] Research Center of the Douglas Mental Health University Institute, Montreal, Québec, Canada
[c] University of Sherbrooke, Department of Psychology, Longueuil, Québec, Canada
[d] McGill University, Department of Educational and Counselling Psychology, Montreal, Québec, Canada
[e] McGill University, Department of Psychiatry, Montreal, Québec, Canada

ARTICLE INFO

Keywords:
Therapy
Propranolol
Reconsolidation
Romantic attachment
Stress

ABSTRACT

Objectives: In a sustained relationship, romantic betrayal is a catastrophic event that can precipitate an adjustment disorder (AD). Surprisingly, there exists no empirically validated treatment for AD, despite its high prevalence in clinical practice. Considering the promise of memory reactivation under propranolol (i.e., reconsolidation interference) for treating posttraumatic stress disorder, we sought to extend this finding to AD, given that in both disorders, symptoms stem from an identified stressor.

Method: A single-blind interrupted time series design was used to examine the efficacy of memory reactivation under propranolol to alleviate symptoms of AD. After being placed on a 4-week waitlist, sixty-one participants received 5 weekly 25-min treatments during which they recalled the betrayal event, 1 h after having orally ingested the beta-blocker propranolol.

Results: Segmented regression analyses on the intent-to-treat sample revealed that AD symptoms significantly decreased during the treatment phase (pre/post Cohen's $d = 1.44$), compared to the waitlist phase ($d = 0.01$). Significant pre/post reductions in anxio-depressive symptomatology were also found. Improvement was maintained at the 4-month follow-up on all outcomes.

Conclusion: Memory reactivation under propranolol shows promise in reducing symptoms of AD. This study provides the theoretical framework and necessary effect sizes to inform larger, double-blind, placebo-controlled clinical trials.

Betrayals in committed romantic relationships, such as infidelity, an act of deception, or sudden abandonment, are common occurrences that can have profound consequences for individual mental health and couple well-being (Gordon et al., 2015; Johnson et al., 2001). Taking just one example of romantic betrayal, conservative estimates indicate that infidelity affects up to a quarter of marriages, and even higher rates have been reported in non-marital dating relationships (Fincham and May, 2017). Betrayal by a loved one shatters the assumptions of safety and trust that underlie secure romantic bonds, and as such, can lead to prolonged emotional turmoil for the betrayed partner and relationship breakdown (Hall and Fincham, 2006; Johnson et al., 2001; Lonergan et al., 2021). Over the last two decades, investigators have increasingly recognized the commonalities between post-betrayal distress and certain forms of psychological trauma (Johnson et al., 2001; Lonergan et al., 2021; Whisman and Wagers, 2005). Evidence suggests that romantically betrayed individuals often report clinically important event-related stress symptoms, not unlike posttraumatic stress disorder (PTSD), such as intrusions, avoidance, hyperarousal/hypervigilance, negative cognitions, as well as depressed mood and anxiety, all of which have deleterious effects on quality of life and social functioning (Laaser et al., 2017; Roos et al., 2019; Steffens and Rennie, 2006; Whisman, 2015). Importantly, there is an unmet need for brief innovative

☆ Clinicaltrial.gov: NCT03151681.

* Corresponding author.
E-mail address: alain.brunet@mcgill.ca (A. Brunet).

https://doi.org/10.1016/j.jad.2022.08.082
Received 19 November 2021; Received in revised form 25 May 2022; Accepted 22 August 2022
Available online 27 August 2022

interventions that target this symptomatology.

Adjustment disorder (AD), part of the trauma- and stressor-related disorders category in the *Diagnostic and Statistical Manual for Mental Disorders* (DSM-5; American Psychiatric Association [APA], 2013), allows for contextualizing the psychological sequela of romantic betrayal. AD is a maladaptive emotional and behavioral response to a critical life stressor, such as job loss or divorce. Its core clinical symptoms overlap largely with those of PTSD and include intrusive thoughts of the painful life experience, in addition to avoidance, anxio-depressive symptoms, and functional impairment. However, in sharp contrast to PTSD, the precipitating stressor of AD – no matter how serious – can never involve a life threat, serious bodily injury, or sexual violence (i.e., Criterion A; APA, 2013; Maercker and Lorenz, 2018). While the conditional risk for developing AD due to romantic betrayal remains unknown, AD ranges from 5 to 20 % in primary care settings and affects 1–2 % of the general population (Maercker et al., 2012; Zelviene and Kazlauskas, 2018). Although AD is presumed to be limited to 6 months in duration (APA, 2013), it may prolong beyond that time (Maercker et al., 2012). As AD, particularly if protracted, can be associated with increased risk for progression into further pathology (O'Donnell et al., 2016), effective interventions are needed.

1. Etiology of AD: shattered assumptions, emotional memory, and the role of betrayal

Emotional events, like romantic betrayals, are better remembered (in part) due to increased activation of endogenous stress hormones during and after initial learning, which potentiates memory consolidation (i.e., the stabilization of memories into long-term storage) and facilitates recall (McGaugh, 2013). For some individuals, activation of these mechanisms when exposed to threatening stimuli may create an overly consolidated emotional memory of the stressful event that is subsequently too easily activated when confronted with reminder cues (McGaugh, 2013; Pitman, 1989). This perpetuates event-related stress that may manifest in the form of intrusive re-experiencing, avoidance, and increased vigilance (Brewin et al., 2010; Marks et al., 2018). To account for clinical heterogeneity in trauma- and stress-related responses, psychological theories, including attachment theory (Atkinson and Zucker, 1997), emphasize the role of the subjective meaning of the stressor. Event-related stress symptoms are argued to arise following experiences that threaten positive views of the self as competent or lovable, others as trustworthy, and the world as safe and predictable, or conversely, when such experiences confirm negative worldviews (Brewin et al., 2010; Horowitz, 1986; Maercker et al., 2007). Thus, core event-related stress symptoms associated with AD may be conceptualized as rooted in an overly consolidated emotional memory of the precipitating stressor combined with maladaptive appraisals of the cause and consequences of the event (e.g., overgeneralization of danger, shame, self-blame, sense of 'going crazy' or damaged future; Brewin et al., 2010; Ehlers and Clark, 2000; Marks et al., 2018).

According to predominant frameworks, traumatic events leading to a PTSD diagnosis involve life-threat and intense fear. Arguably, betrayal events also involve fear insofar as they threaten the safety and stability of the social attachment system, which is as fundamental to human survival as physical safety (Eisenberger and Cole, 2012; Johnson et al., 2001). The neural circuits that underlie fear- or physical threat-related emotional memories are also activated when one experiences personal deception (Grezes et al., 2006) or is presented with reminders of unrequited love (Fisher et al., 2010). In support of this notion, research (Laaser et al., 2017; Roos et al., 2019; Steffens and Rennie, 2006) reveals that 30–60 % of betrayed individuals report clinically significant symptoms on the Impact of Event Scale — Revised (IES-R; Weiss and Marmar, 1997), a widely used measure of event-related stress symptoms (intrusions, avoidance, hypervigilance). Recently, Roos et al. (2019) examined the association between discovering a partner's infidelity and IES-R scores in a sample of 73 undergraduates: 45 % scored above the measure's clinical threshold indicative of possible PTSD (Creamer et al., 2003). These scores were associated with depressive symptoms, even after controlling for prior trauma exposure. Others found that betrayal was uniquely predictive of major depression and generalized anxiety in the betrayed partner, in addition to negative event-related cognitions (e.g., "I will never recover emotionally from the pain and devastation of the betrayal"; Laaser et al., 2017, p. 439; Whisman, 2015). Thus, romantic betrayals can precipitate psychological distress that is consistent with an AD and this distress can be measured reliably with psychometrically valid scales.

2. Treatments for AD: limitations and new avenues

Despite being considered the 'common cold' of psychiatry, there has been a paucity of investigations of AD in general, which explains the lack of evidence-based treatments. Bearing in mind that AD is supposed to 'go away' within 6 months (APA, 2013), brief and supportive psychotherapy is recommended as a first-line intervention (O'Donnell et al., 2018). However, supportive psychotherapy requires an intense personal investment, and its efficacy for AD remains, at best, tentative (O'Donnell et al., 2018; Zelviene and Kazlauskas, 2018). Interventions geared toward the unique effects of betrayal have shown promise (Gordon et al., 2015; Johnson, 2019; Kroger et al., 2012; Makinen and Johnson, 2006), but they typically involve both partners, a constraint which does not meet the needs of some betrayed clients. Finally, psychotropic drugs may be used in the treatment of AD. However, they only offer a palliative approach that masks symptoms without targeting the underlying pathology; they must be taken daily for an unknown – often prolonged – amount of time, with ensuing side-effects that can lead to noncompliance and relapse (Sansone and Sansone, 2012). Thus, investigations into empirically based treatments for trauma-and stressor-related disorders beyond PTSD are warranted.

Inasmuch as AD represents a *forme fruste* of PTSD without the life threat, one intervention that has yet to be investigated rests on reconsolidation theory. This theory suggests that memory reactivation (i.e., retrieval) can destabilize a previously consolidated emotional memory, subsequently inducing a transient period of lability during which time the trace must reconsolidate (i.e., restabilize) back to long-term storage in order to persist (Elsey et al., 2018). As in initial consolidation, the reconsolidation of emotional memories involves the reactivation of the noradrenergic system within the amygdala and de novo protein synthesis (Lee et al., 2017; Lim et al., 2018; Nader et al., 2000). Reconsolidation theory offers new hope for the treatment of trauma- and stressor-related disorders: when used in conjunction with an active memory retrieval procedure, the lipophilic noradrenergic beta-blocker propranolol dampens the enhancement of memory conferred by emotion, presumably by disrupting the reconsolidation processes (Lee et al., 2017; Lonergan et al., 2013). Brunet et al. (2018) recently showed that six 25-min sessions of trauma reactivation under propranolol alleviated PTSD symptoms compared to the same reactivation procedure under placebo. Further evidence of its therapeutic potential comes from studies of spider phobia (Soeter and Kindt, 2015), substance dependence (Lonergan et al., 2016), and meta-analyses examining memory reactivation under propranolol vs. placebo in healthy volunteers and clinical samples (Lonergan et al., 2013; Pigeon et al., 2022).

Memory reactivation under propranolol remains an entirely new, unexplored therapeutic method with respect to AD that has never been tried before. This manuscript presents the results of the first clinical trial examining whether memory reactivation under propranolol can successfully alleviate AD symptoms, as is the case for PTSD (Brunet et al., 2018).

3. Method

3.1. Study design and hypothesis

In a single-blind interrupted time series design, participants received an eligibility assessment (Week 0: W0), a 4-week waitlist period (pre-intervention phase: W0–W4), 5 once-a-week treatment sessions (intervention phase: W4–W8), and a post-treatment assessment (W9; see Table 1). Compared to the waitlist phase, it was hypothesized that the severity of event-related stress symptoms would significantly reduce during the intervention phase. Within-group changes in specific symptom domains (i.e., intrusions, avoidance, and hypervigilance), as well as in general anxio-depressive symptoms, were also explored. Finally, the persistence of treatment effects at a 4-month follow-up were examined, considering that this is a significant problem in other treatment modalities (O'Donnell et al., 2018). This trial was approved by the Douglas Institute Research and Ethics Board (#15-07) and a no objection letter was obtained from Health Canada (#183228).

3.2. Participants

Eligible participants were adults (18–65 years old) meeting the DSM-5 AD criteria, as determined by a structured clinical interview (Mini International Neuropsychiatric Interview [MINI]; Sheehan, 2016), as well as by severity of past-week event-related stress (total score > 24 on the IES-R; Asukai et al., 2002). The identified stressor needed to correspond to a betrayal event (infidelity or sudden abandonment) that occurred in the context of a committed, monogamous long-term relationship of at least 6 months in duration. The exclusion criteria, as in Brunet et al. (2018), included: basal systolic blood pressure < 100 mmHg, basal cardiac rhythm < 55 bpm, pregnancy/breast-feeding, psychotropic medication use, a medical contraindication related to propranolol, current psychiatric comorbidity, or active self-harm/suicidality. The receipt of supportive counselling while on the waitlist was tolerated as long as it was documented and the counselling sessions did not directly target the betrayal event. It was deemed that this would not facilitate rejection of the null hypothesis. Moreover, supportive counselling was suspended during the treatment phase of the study for all participants.

3.3. Outcome measures

In line with prior work (Kroger et al., 2012; Roos et al., 2019), the 22-item self-report IES-R (Weiss and Marmar, 1997) was used as the primary clinical outcome to assess event-related symptom severity over the past 7 days among the betrayed/abandoned participants. This widely used and well-validated measure includes three subscales: intrusions (7 items), avoidance (8 items), and hyperarousal (7 items). Internal consistency for the subscales ranges from 0.79 to 0.94 (Creamer et al., 2003; Weiss and Marmar, 1997). A severity score is obtained by summing all items (range: 0–88); 33 is a widely used clinical cut-off score for possible PTSD (Creamer et al., 2003). The IES-R was administered at baseline, during the waitlist phase, at each treatment visit, as well as at post-treatment and follow-up. As a secondary outcome, participants also completed the self-report Hopkins Symptom Checklist-25 (HSCL-25; Winokur et al., 1984). This measure provides a total severity score (mean of items), as well as two subscale scores: depression (15 items) and anxiety (10 items). A mean score of 1.75 distinguishes clinical from non-clinical populations (Mattisson et al., 2013). The HSCL-25 is a well-validated measure, with Cronbach's alphas of 0.89 and 0.87 for the depression and anxiety subscales, respectively, and 0.93 for the overall measure (Nabbe et al., 2019). This measure was administered at baseline, at each treatment visit, as well as at post-treatment and follow-up.

Table 1
Study design and timeline for administration of the IES-R.

Week	Phase
W0 — Baseline	Pre-intervention
W2 — Waitlist	Pre-intervention
W4 — Treatment 1	Pre-intervention (intervention starts)
W5 — Treatment 2	*Effect of 1 intervention (change in level immediately post-intervention)*
W6 — Treatment 3	Effect of 2 interventions
W7 — Treatment 4	Effect of 3 interventions
W8 — Treatment 5	Effect of 4 interventions
W9 — Post-treatment	*Effect of 5 interventions (change in level after 5 interventions)*

3.4. Procedure

Candidate participants were screened by phone using a brief standardized interview procedure designed to explain the purpose of the study and to identify any apparent exclusion criteria (e.g., diagnosed asthma, diabetes, a history of cardiovascular problems, a history of bipolar disorder or schizophrenia, or the use of psychotropic medication). Apparently eligible individuals were invited to the Douglas Institute for a comprehensive face-to-face eligibility assessment. Written informed consent was obtained from all participants prior to the assessment. Next, data on participants' sociodemographic characteristics and relationship history were collected, and a structured clinical interview (the MINI-S; see above) was conducted by a trained graduate student. Participants completed the IES-R and HSCL-25 prior to being evaluated by the study physicians, who confirmed their diagnosis of AD, ensured that they can safely receive propranolol, and determined if any exclusion criteria were met.

As described elsewhere (Brunet et al., 2018), during the first treatment session, participants received 1 mg/kg of propranolol, under the supervision of a nurse at the Douglas Institute, and then completed the IES-R and HSCL-25. Blood pressure was monitored prior to medicine intake and subsequently every 30 min for 60 min using the Welch Allyn, Spot vital signs device, Masimo set, which is re-calibrated annually and certified. On average, participants' systolic blood pressure dropped by 5.5 % (Baseline $M = 115.0$, $SD = 17.84$; +60 min $M = 108.7$, $SD = 15.53$), suggesting that the drug was adequately metabolized. A dose of 40–80 mg of oral propranolol produces a peak blood level of approximately 100 ng/ml after about 75 min (Dey et al., 1986). Propranolol was ingested with a snack to enhance bioavailability (Melander, 1978). After 60 min, participants began writing a one-page narrative of the betrayal/abandonment event in the first-person present tense, that focused on the most emotionally salient part of the memory and included five physical sensations drawn from a list, which consisted of commonly experienced stress-related reactions (e.g., nausea, feeling tense, hyperventilating, trembling, sweating). The procedure, originally developed by Pitman et al. (1987), has been used in prior reconsolidation studies involving PTSD participants (Brunet et al., 2018).

For the remaining treatment sessions, participants were reminded by phone to take the study drug and a snack at home 60 min prior to their appointment. Upon arrival to the Douglas Institute, participants completed the IES-R and HSCL-25 and then read their event narrative out loud once to the treatment provider. After the reading was completed, participants were asked whether there was a need to add any new/missing detail to the narrative. The most common side-effect of propranolol was mild fatigue ($n = 34$) and gastrointestinal discomfort ($n = 11$), which were all considered tolerable and did not require treatment interruption in any case.

Treatment providers were graduate students, who were formally trained and supervised by the senior author (Reconsolidation Therapy™; see www.reconsolidationtherapy.com). Sessions (10 %) were randomly rated for treatment adherence by a third-party using a homemade adherence measure (Brunet and Lonergan, unpublished manual). Minor protocol deviations were noted in a small number of sessions (e.g., patients writing a narrative in the past tense). Corrective

feedback was immediately provided.

3.5. Statistical analyses

3.5.1. Preliminary analysis

Descriptive statistics were computed for the sociodemographic and clinical variables. For control purposes, participants who had previously received therapeutic interventions, as well as those who were receiving supportive counselling while on the waitlist, were compared to other participants (no prior or current treatment) on the outcome measures using a one-way ANOVA.

3.5.2. Analysis of primary outcome: IES-R total scores over time

Analyses were conducted in the *intent-to-treat* (ITT) sample (Gupta, 2011), which consisted of all included participants ($N = 61$). Multiple imputations were used to account for missing data (7.7 % of values) on the IES-R total scores. Per Little's MCAR test, missing data were considered missing at random ($\chi^2 = 110.58$, $df = 117$, $p = .650$). Additionally, there were no significant differences between treatment dropouts and completers on any baseline variable. Twenty imputed data sets were created to minimize over-estimating the standard errors and reduce bias (Graham et al., 2007). Sociodemographic and clinical variables were included in the imputation model as predictor variables, and data from the IES-R were imputed and used as predictor variables. The Fully Conditional Specification method, which employs an iterative Markov Chain Monte Carlo algorithm using predictor and imputed values at one step to impute missing values in subsequent steps, was used. Constraints were placed to ensure that the imputed values did not exceed the measures' range. Model convergence was achieved.

Segmented regression analyses were used to examine changes in severity of event-related symptoms, measured by total IES-R scores, over time. Specifically, changes in the time trend between the waitlist and intervention phases were compared, and changes in the level of the slopes (i.e., intercepts) after participants received one treatment session and after they received all treatment sessions were examined. The regression coefficient for the time by phase (waitlist vs intervention) interaction represents the difference between slopes and determines whether there is a change in trend over time between phases. The regression coefficient for the level effect at week 5 represents the effect of a single treatment session, and the regression coefficient for the level effect at week 9 represents the effect of 5 treatment sessions. A change in level can be understood as the difference between the intercept of the post-intervention timepoint of interest and the intercept predicted by the pre-intervention slope (Ramsay et al., 2003).

As a sensitivity analysis, a linear mixed-effects model (LMM) was conducted in order to account for the dependence of residuals and explicitly model the covariance structure of the repeated measures within participants. The variables entered as fixed effects were time, phase, and the time by phase interaction. The time by* phase interaction allowed to test if the slopes between the waitlist and treatment phases significantly differed. Random effects for participants' intercepts and slopes were included and modeled using the unstructured covariance structure. Finally, a significant interaction was decomposed by examining the Johnson-Neyman (J-N) region of significance, i.e., the point in time when the predicted treatment levels become significantly different than the predicted pre-intervention slope.

3.5.3. Secondary analyses: IES-R subscale scores, HSCL-25 total and subscale scores, and follow-up data

Repeated measures ANOVAs were conducted as on the IES-R subscale scores and the HSCL-25 total and subscale scores to explore within-group change from baseline (W0) to post-waitlist (W4), and from post-waitlist to post-treatment (W9) in the per protocol sample (i.e., participants who completed all 5 treatment sessions and the post-treatment assessment; $N = 48$). Bonferroni pairwise comparisons were conducted within session time-points and Greenhouse-Geisser corrections were applied when sphericity was violated. Follow-up data was analyzed with Bonferroni-corrected paired *t*-tests between the post-treatment and the 4-month follow-up IES-R and HSCL-25 total scores.

3.5.4. Sample size

Power was calculated a priori for the ITT sample on the IES-R total score using G*Power v.3.1.9.4 indicated that 54 participants were needed to detect an effect of $f^2 = 0.25$ with 85 % power and a two-sided alpha of 0.05. This effect is approximately equivalent to a reduction of 1SD or a 15-point drop on IES-R total score (Coffey et al., 2016).

4. Results

In all, 61 participants were included in the ITT sample (see Table 2 for the sample's sociodemographic and baseline clinical data); 55 returned to the first treatment session after being placed on the waiting list and 48 completed all 5 sessions and the post-treatment visit (i.e., the per protocol sample), speaking to the high treatment tolerability (Fig. 1). As indicated in Table 2, 36 participants reported having previously engaged in other forms of therapy following the event, of which 11 participants were receiving supportive counselling while on the waitlist; 24 participants had never engaged in other psychotherapeutic interventions. No significant differences between these groups were found on any measured variables (IES-R: Baseline $F_{(2,57)} = 0.43$, $p = .651$, $\eta^2 = 0.02$; Post-treatment $F_{(2,44)} = 0.07$, $p = .937$, $\eta^2 < 0.01$; HSCL-25: Baseline $F_{(2,57)} = 0.52$, $p = .597$, $\eta^2 = 0.02$; Post-treatment $F_{(2,44)} = 0.52$, $p = .598$, $\eta^2 = 0.02$). This variable was therefore not included as a covariate in subsequent analyses.

In this sample, 20 participants had experienced one or more traumatic events in their lifetime, such as: experiencing, witnessing, or learning about a car accident ($n = 6$), a work-related accident ($n = 1$), physical assault ($n = 3$), intimidation ($n = 1$), political violence ($n = 1$), the sudden death of a loved one ($n = 4$), or learning about sexual assault having occurred to a significant other ($n = 2$); five participants chose to not disclose the event. Three participants had a lifetime diagnosis of PTSD; all were currently in remission.

Table 2
Sociodemographic and clinical characteristics of the Sample.

Characteristic	Participants ($n = 61$)	
	M	*SD*
Age	42.77	12.76
Education (years)	17.02	2.62
Time since betrayal event (years)	3.87	5.83
Duration of relationship (years)	9.77	10.75
	N	**%**
Gender (% women)	44	72.13
Ethnicity (% Caucasian)	53	86.89
Annual income (≥50k CAD$)	30	49.21
Marital status (single)	40	66.57
Betrayal event		
Infidelity/deception	43	70.49
Sudden abandonment	18	29.51
Prior mental health service use	36	59.01
Current supportive counselling	11	18.03
Comorbidity		
Lifetime major depression (not past month)	27	44.26
Lifetime anxiety disorder (not past month)	18	29.51
IES-R[a] symptom improvement waitlist phase		
Moderate to none	50	90.91
Clinically meaningful[b]	5	9.10
IES-R symptom improvement treatment phase		
Moderate to none	7	14.58
Clinically meaningful[b]	41	85.42

[a] IES-R = Impact of Event Scale-Revised.
[b] A reduction of ≥15 points (1SD) on the IES-R from pre to post waitlist $N = 55$; post-waitlist to post-treatment $N = 48$.

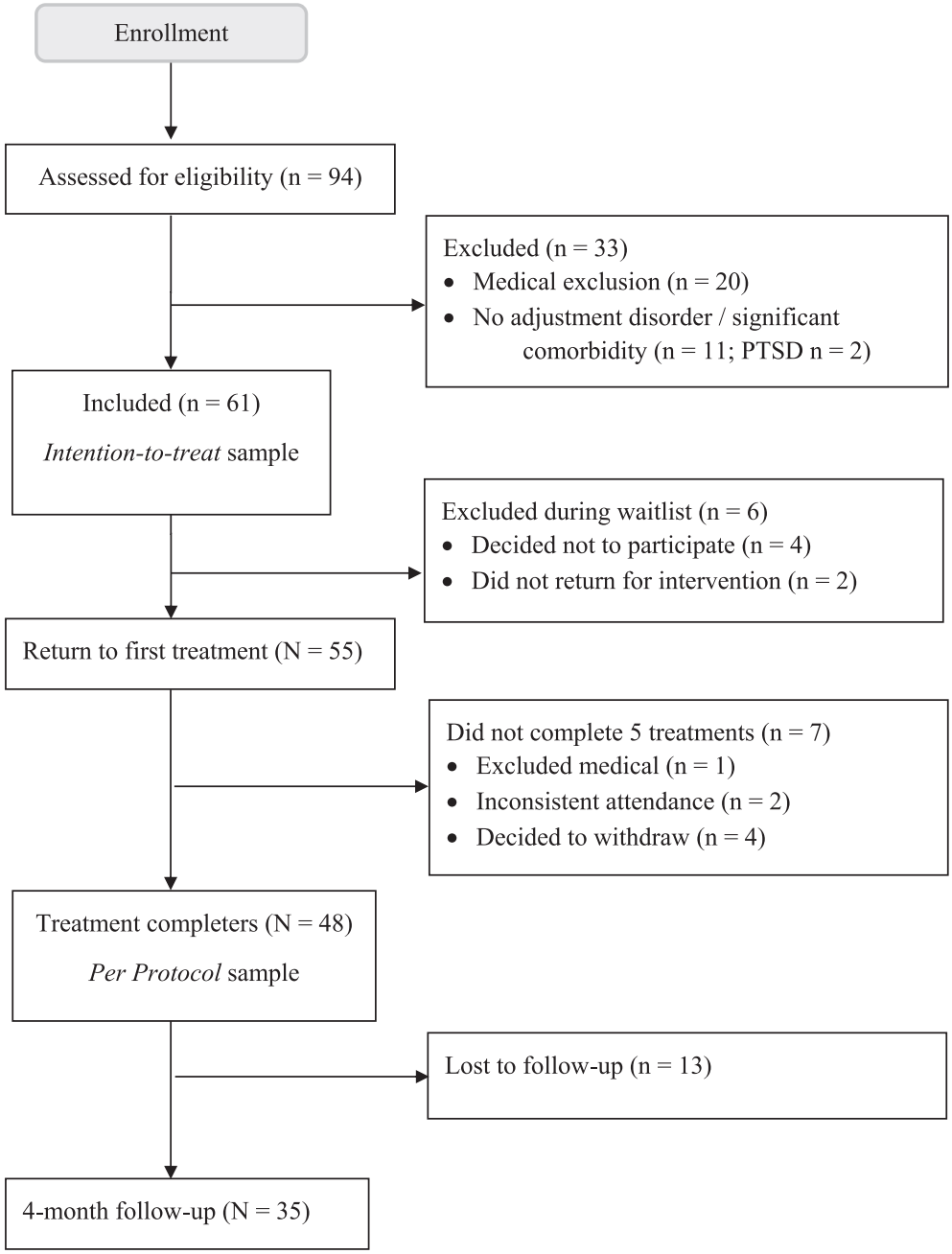


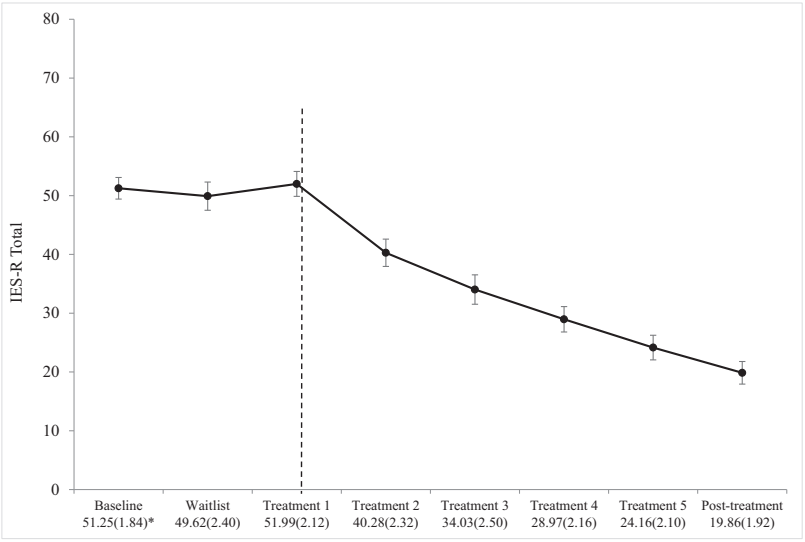
Fig. 1. Participant flowchart.

4.1. *Effects of treatment on event-related symptom reduction*

In line with the Cochrane Effective Practice and Organization of Care (CEPOC, 2017) recommendations, and considering a significant Ljung Box Q statistic for an uncorrected model ($Q = 664.88$, $df = 18$, $p < .001$), an Auto Regressive Integrated Moving Average (ARIMA) model that corrects for first-order autocorrelation was used for the segmented regression analyses. The corrected ARIMA model demonstrated better fit than the uncorrected model, as indicated by a non-significant Ljung Box Q statistic ($Q = 25.64$, $df = 17$, $p = .081$), as well as a lower normalized Bayesian Information Criterion (BIC) value (BIC uncorrected model = 5.48; BIC corrected model = 4.76). Results, depicted in Fig. 2. and Table 3, indicated a significant difference between the waitlist and intervention slopes (i.e., time * phase interaction). During the waitlist phase, there was no significant change in IES-R scores. There was a large significant drop in IES-R scores immediately following the first intervention, and IES-R scores continued to significantly decline over time during the intervention phase. The level effect at Week 9 (i.e., after 5 interventions) was also significant.

Similar results were obtained from the LMM analysis. More specifically, there was a significant time * phase interaction ($F_{1, 364} = 113.88$, $B = -5.26$, $SE = 0.49$, $p < .001$, 95%CI = −6.23; −4.29). During the waitlist phase, there was no significant change in IES-R scores over time ($B = 0.19$, $SE = 0.42$, $p = .661$, 95%CI = −0.65; 1.02). During the treatment phase, there was a significant reduction in IES-R scores over time ($B = -5.07$, $SE = 0.39$, $p < .001$, 95%CI = −5.83; −4.30), which began immediately after participants received the first treatment.

Within subjects paired effect sizes were computed on the non-imputed data using the pooled standard deviation as the denominator and accounting for the intercorrelation between time points (see Lakens, 2013). The means and standard deviations used for the computing the effect sizes were as follows: Waitlist phase ($n = 55$) W0 $M = 51.12$, $SD =$



* IES-R = Impact of Event Scale-Revised. Values represent Mean (SE) total IES-R scores at each week. The beginning of intervention phase is depicted by the dotted line.

Fig. 2. IES-R scores over time in the ITT sample ($N = 61$).

Table 3
Results from the segmented regression analysis on IES-R Total Scores ($N = 61$), corrected for first order autocorrelation.

Effect	Estimate (*B*)	*SE* (*B*)	*t*	95 % CI of *B*		*p*
				LL	UL	
Waitlist phase time	0.15	0.45	0.33	−1.28	1.58	.743
Treatment phase time	−5.17	0.52	−10.02	−6.82	−3.52	<.001
Time * Phase	−5.32	0.85	−6.25	−8.02	−2.61	<.001
Level effect W5	−11.93	1.59	−7.50	−16.99	−6.87	<.001
Level effect W9	−33.20	3.98	−8.35	−45.87	−20.53	<.001

14.80 and W4 $M = 50.98$, $SD = 16.07$; Treatment phase ($n = 48$) W4 $M = 50.58$, $SD = 16.56$ and W9 $M = 17.98$, $SD = 13.30$. The pre-post effect size for the waitlist phase was $d = 0.01$ ($r = 0.71$), and for the treatment phase was $d = 1.44$ ($r = 0.25$), a very large effect by conventional standards (Cohen, 1992).

4.2. Effects of treatment on event-related symptom reduction: IES-R subscales

Results from the repeated measures ANOVAs on IES-R subscale scores in the per protocol sample ($N = 48$; see Fig. 1) indicated a significant main effect of time for the Intrusion subscale ($F_{1.71,\ 80.54} = 114.13$, $p < .001$, $\eta^2 = 0.71$), the Avoidance subscale ($F_{1.47,\ 68.99} = 75.23$, $p < .001$, $\eta^2 = 62$), and the Hypervigilance subscale ($F_{2,\ 94} = 66.99$, $p < .001$, $\eta^2 = 0.59$). Post-hoc pairwise Bonferroni comparisons revealed no significant differences in any subscale scores between baseline- and post-waiting list (all $ps > .999$), and significant reductions in all subscale scores between post-waiting list and post-treatment (all $ps < .001$), and between baseline and post-treatment (all $ps < .001$; Table 4).

4.3. Effects of treatment on anxio-depressive symptoms

Results from the repeated measures ANOVAs on general anxio-depressive symptoms indicated a significant main effect of time for HSCL-25 total scores ($F_{2,\ 92} = 66.99$, $p < .001$, $\eta^2 = 0.59$), as well as the Depression subscale ($F_{2,\ 92} = 73.02$, $p < .001$, $\eta^2 = 0.61$) and the Anxiety subscale ($F_{2,\ 94} = 31.64$, $p < .001$, $\eta^2 = 0.40$). Post-hoc pairwise Bonferroni comparisons revealed no significant differences between baseline- and post-waiting list for the total and subscale scores (all $ps \geq .999$), and significant reductions in all scores between post-waiting list and post-treatment (all $ps < .001$), and between baseline and post-treatment (all $ps < .001$; Table 4).

4.4. The persistence of treatment effects

Thirteen participants were lost to follow-up, resulting in 35 participants with data at the post-treatment and follow-up assessment, and the average time elapsed between post-treatment and follow-up was 4 months ($SD = 0.89$). There were no significant within-group differences for the treated group on total IES-R total scores (post-treatment $M = 17.77$, $SD = 11.21$; follow-up $M = 18.87$; $SD = 15.34$, $t_{34} = -0.46$, $p =$

Table 4
Means, standard deviations, and within-group effect sizes for IES-R Subscale Scores and HSCL-25 total and subscale scores ($n = 48$).

Measure	Baseline Week 0		Post-waiting list Week 4			Post-treatment Week 9		
	M	*SD*	*M*	*SD*	*d*[a]	*M*	*SD*	*d*[b]
HSCL-25 Total	2.13	0.49	2.16	0.56	−0.07	1.47	0.48	1.49
HSCL-25 Depression	2.39	0.57	2.46	0.66	−0.18	1.60	0.59	1.56
HSCL-25 Anxiety	1.73	0.46	1.75	0.54	−0.05	1.28	0.35	1.09
IES-R Intrusion	21.84	6.72	21.83	7.32	<0.01	7.70	6.71	1.52
IES-R Avoidance	16.71	6.24	16.90	6.99	−0.07	6.79	5.56	1.06
IES-R Hypervigilance	12.19	5.91	11.85	6.08	0.08	3.48	3.95	1.19

[a] Reflects within-group effect size from baseline to post-waiting list.
[b] Reflects within-group effect size from post-waiting list to post-treatment.

.649), on HSCL-25 total scores (post-treatment $M = 1.40$, $SD = 0.39$; follow-up $M = 1.42$, $SD = 0.49$; $t_{32} = -0.63$, $p = .534$), suggesting the achieved symptom improvement endured up to 4 months.

5. Discussion

This is the first study to investigate the efficacy of memory reactivation under propranolol to treat AD. Among participants with an AD stemming from romantic betrayal, results revealed statistically significant and clinically meaningful decreases in event-related stress symptoms in five 25-min sessions, and as early as the first session, when compared to a waitlist phase, during which participants had not improved. A rapid reduction in specific event-related symptom clusters (intrusions, avoidance, hypervigilance), as well as general anxio-depressive symptoms, was also observed. These findings align with prior research suggesting that a single reactivation session under propranolol can produce notable decreases in emotional responses to stressors (Brunet et al., 2008; Soeter and Kindt, 2015), and additional sessions may have additive effects (Brunet et al., 2018). The treatment protocol was well tolerated as documented by a low drop-out rate, and treatment gains were maintained at the follow-up, suggesting a sustained effect lasting up to at least 4-months even after treatment is discontinued.

Findings from this study add considerably to the literature on AD and its treatment, as well as on the psychological impact of betrayals by a romantic partner (Lonergan et al., 2021). Maercker et al. (2007) conceptualize AD as a stress-response syndrome (see also Horowitz, 1986) characterized by core symptoms of intrusions/preoccupations/avoidance and failure to adapt, which has been recently adopted in the 11th edition of the *International Classification of Diseases* (Maercker and Lorenz, 2018; World Health Organization, 2018). Consistent with this, most participants in this study not only exceeded the clinical cut-off of the IES-R at study entry, but total and subscale scores were similar to other populations suffering from PTSD, as indicated in prior research (e.g., Rash et al., 2008; note that this was not formally tested). Likewise, scores on the HSCL-25 were similar to clinical populations with diagnosed mood or anxiety disorders, particularly for depression (Mattisson et al., 2013), and these symptoms were also substantially alleviated at post-treatment. Intrusive symptoms were an important problem in this sample, and notably, they were the most improved. Such findings are not only in line with prior literature on the psychological effects of romantic partner betrayal (Johnson et al., 2001; Lonergan et al., 2021; Roos et al., 2019; Whisman, 2015), but also with the notion that intrusions/preoccupations are a core symptom in all stressor-related disorders and represents an important transdiagnostic therapeutic target (Marks et al., 2018), for which memory reactivation under propranolol can be suitable for.

5.1. Limitations and future directions

The within-subjects open-label design of the current study was purposely chosen, as it was deemed necessary to provide to theoretical and methodological building blocks that are required for the conceptualization and design of larger trials in an understudied clinical population, such as those with AD. However, several limitations of this study should be noted.

First, research suggests that placing treatment-seeking individuals on a waiting list in clinical trials may stall their natural progression as they 'wait' to change (Cunningham et al., 2013; Mohr et al., 2009), producing upward biases in treatment effects when compared to an independent, parallel group who immediately receives the intervention. Yet because of the within-subjects waitlist design of the current study, this threat to internal validity may have been minimized, as any between-group variability would have been reduced. Relatedly, the average time since the betrayal event was approximately four years in this sample, suggesting little effect of time alone on symptom improvement or change.

Second, as the underlying mechanisms of change were not examined, the observed treatment gains cannot be attributed to reconsolidation interference per se. Without a placebo group (with and without memory reactivation) or a propranolol plus no-memory reactivation group within a randomized trial, the possibility that treatment effects were obtained due to other uncontrolled reasons cannot be ruled out. For instance, reconsolidation-based interventions involve writing and reading a narrative of the stressful experience under the influence of the reconsolidation blocker propranolol, with the guidance of an empathetic treatment provider. This 'exposure' process, in addition to other common factors in psychotherapy (e.g., clinical attention; Wampold, 2015), could, at least in part, explain the results. However, in a very similar study by Brunet et al. (2018), reading one's trauma narrative once under placebo on 6 weekly occasions was not sufficient to bring about significant clinical change for participants with PTSD.

It is also important to note that the memory reactivation procedure used in clinical reconsolidation protocols, including that of the current study, is purposely kept brief in order to maximize the likelihood of triggering memory destabilization and reconsolidation, while minimizing (although not completely eradicating) extinction effects that may occur with prolonged exposure to triggering material (Finnie and Nader, 2012). In contrast to the reconsolidation process, which can be understood as an 'update' mechanism, extinction learning, the mechanism by which exposure-based psychotherapies are arguably based on, involves the creation and consolidation of a new independent memory trace that competes with the original memory for dominance (Elsey et al., 2018). In line with this, it has been proposed that the blockade of noradrenergic signaling conferred by propranolol may interfere with the consolidation of extinction learning induced by longer exposures (Mueller and Cahill, 2010), which may result in a reduced (or no) treatment effect. Thus, as extinction learning may prevent the destabilization and reconsolidation of the original trace from occurring (Finnie and Nader, 2012), and considering that the within-group intervention effect size found in the current study ($d = 1.44$) is similar in magnitude to the same effect reported in Brunet et al.'s (2018) placebo-controlled trial ($d = 1.76$), results from this study appear congruent with reconsolidation theory.

Third, to remain consistent with prior research in similar populations (e.g., Roos et al., 2019), a self-report measure of event-related distress was used (the IES-R) as the primary outcome, which may over-estimate symptom severity (Monson et al., 2004). However, this would not have necessarily affected the observed pre/post contrasts. Additionally, considering the role of attachment in post-trauma pathology (Charuvastra and Cloitre, 2008), betrayal or abandonment by a romantic partner may be associated with a specific type of AD and other relevant indicators of adjustment that were not addressed in the current study, such as perceived quality of life, impacts on other significant attachments, and worldviews, for instance. Finally, the sample was comprised of predominantly Caucasian, well-educated individuals in heterosexual relationships who largely reported infidelity-related betrayal events, which limits generalizability, and the follow-up period was relatively short. Future studies using additional controls over a longer follow-up period, in addition to including structured diagnostic assessments of AD and various measures of adjustment with more diverse samples, are needed to further elucidate the role of romantic betrayal in precipitating an AD, and to expand on our findings concerning the treatment of AD.

6. Conclusion

This paper is the first to address the unmet need for an empirically validated treatment for AD, namely with memory reactivation under propranolol. As such, this study provides the required theoretical and methodological blueprint for the planning and execution of randomized trials that include additional control conditions. Such studies are needed, as AD is a psychological disorder that remains a highly prevalent, yet largely understudied (Brunet et al., 2022). Pending future

studies, this intervention has the potential to help alleviate the 'common cold' of psychiatry much faster than by simply letting it run its presumed course.

Funding

M.L. received a doctoral award from the *Fonds de Recherche du Québec - Santé, Québec Canada* while working on this project, and currently holds a postdoctoral award from the *Social Sciences and Humanities Research Council of Canada*.

Ethics

Approval was obtained from the ethics committee of Douglas Institute. The procedures used in this study adhere to the tenets of the Declaration of Helsinki. (IRB#15-07).

Availability of data and materials

Requests to access the datasets should be addressed to Alain Brunet (alain.brunet@mcgill.ca).

CRediT authorship contribution statement

Michelle Lonergan: Conceptualization, Supervision, Writing – original draft, Formal analysis, Data curation. **Daniel Saumier:** Conceptualization, Investigation, Writing – original draft, Writing – review & editing. **Sereena Pigeon:** Investigation, Data curation, Project administration, Writing – original draft, Writing – review & editing. **Pierre E. Etienne:** Supervision. **Alain Brunet:** Conceptualization, Supervision, Writing – original draft, Formal analysis, Data curation.

Declaration of competing interest

The treatment procedure described above has been trademarked under the name Reconsolidation Therapy™ by Alain Brunet, who offers an online training in this approach for a fee. See www.reconsolidationtherapy.com. The authors report no other conflicts of interest.

Acknowledgements

We thank the study participants, as well as the local media for their support during recruitment. We also thank Dr. David Streiner, the statistical consultant. Preliminary results were presented at the International Society for Traumatic Stress Studies annual conference (2017; 2019), and the International Congress of Applied Psychology (2018).

References

American Psychiatric Association, 2013. Diagnostic and statistical manual of mental disorders. In: DSM-5®, 5th ed. Author, Arlington, VA.

Asukai, N., Kato, H., Kawamura, N., Kim, Y., Yamamoto, K., Kishimoto, J., Miyake, Y., Nishizono-Maher, A., 2002. Reliabiligy and validity of the Japanese-language version of the impact of event scale-revised (IES-RJ): four studies of different traumatic events. J. Nerv. Ment. Dis. 190 (3), 175–182. https://doi.org/10.1097/00005053-200203000-00006.

Atkinson, L., Zucker, K.J., 1997. Attachment And Psychopathology. Guilford Press, New York.

Brewin, C.R., Gregory, J.D., Lipton, M., Burgess, N., 2010. Intrusive images in psychological disorders: characteristics, neural mechanisms, and treatment implications. Psychol. Rev. 117 (1), 210–232. https://doi.org/10.1037/a0018113.

Brunet, A., Orr, S.P., Tremblay, J., Robertson, K., Nader, K., Pitman, R.K., 2008. Effect of post-retrieval propranolol on psychophysiologic responding during subsequent script-driven traumatic imagery in post-traumatic stress disorder. J. Psychiatr. Res. 42 (6), 503–506. https://doi.org/10.1016/j.jpsychires.2007.05.006.

Brunet, A., Rivest-Beauregard, M., Lonergan, M., Cipolletta, S., Rasmussen, A., Meng, X., Jaafari, N., Superka, J., Brown, A., Sapkota, R., 2022. PTSD is not the emblematic disorder of the COVID-19 pandemic; adjustment disorder is. BMC Psychiatry 22, 300. https://doi.org/10.1186/s12888-022-03903-5.

Brunet, A., Saumier, D., Liu, A., Streiner, D.L., Tremblay, J., Pitman, R.K., 2018. Reduction of PTSD symptoms with pre-reactivation propranolol therapy: a randomized controlled trial. Am. J. Psychiatry 175 (5), 427–433. https://doi.org/10.1176/appi.ajp.2017.17050481.

Charuvastra, A., Cloitre, M., 2008. Social bonds and posttraumatic stress disorder. Annu. Rev. Psychol. 59, 301–328. https://doi.org/10.1146/annurev.psych.58.110405.085650.

Cochrane Effective Practice and Oragnisation of Care (EPOC), 2017. Interrupted Time Series (ITS) Analyses. EPOC Resources for Review Authors.

Coffey, S.F., Schumacher, J.A., Nosen, E., Littlefield, A.K., Henslee, A.M., Lappen, A., Stasiewicz, P.R., 2016. Trauma-focused exposure therapy for chronic posttraumatic stress disorder in alcohol and drug dependent patients: a randomized controlled trial. Psychol. Addict. Behav. 30 (7), 778–790. https://doi.org/10.1037/adb0000201.

Cohen, J., 1992. Quantitative methods in psychology: A power primer. Psychol. Bull. 112 (1), 155.

Creamer, M., Bell, R., Failla, S., 2003. Psychometric properties of the impact of event scale—revised. Behav. Res. Ther. 41 (12), 1489–1496. https://doi.org/10.1016/j.brat.2003.07.010.

Cunningham, J.A., Kypri, K., McCambridge, J., 2013. Exploratory randomized controlled trial evaluating the impact of a waiting list control design. BMC Med. Res. Methodol. 13 (1), 150. https://doi.org/10.1186/1471-2288-13-150.

Dey, M., Brisson, J., Davis, G., Enever, R., Pray, K., Zaim, B., Dvornik, D., 1986. Relationship between plasma propranolol concentration and dose in young, healthy volunteers. Biopharm. Drug Dispos. 7 (2), 103–111. https://doi.org/10.1002/bdd.2510070202.

Ehlers, A., Clark, D.M., 2000. A cognitive model of posttraumatic stress disorder. Behav. Res. Ther. 38 (4), 319–345. https://doi.org/10.1016/S0005-7967(99)00123-0.

Eisenberger, N.I., Cole, S.W., 2012. Social neuroscience and health: neurophysiological mechanisms linking social ties with physical health. Nat. Neurosci. 15 (5), 669. https://doi.org/10.1038/nn.3086.

Elsey, J.W., Van Ast, V.A., Kindt, M., 2018. Human memory reconsolidation: a guiding framework and critical review of the evidence. Psychol. Bull. 144 (8), 797–848. https://doi.org/10.1037/bul0000152.

Fincham, F.D., May, R.W., 2017. Infidelity in romantic relationships. Curr. Opin. Psychol. 13, 70–74. https://doi.org/10.1016/j.copsyc.2016.03.008.

Finnie, P.S., Nader, K., 2012. The role of metaplasticity mechanisms in regulating memory destabilization and reconsolidation. Neurosci. Biobehav. Rev. 36 (7), 1667–1707. https://doi.org/10.1016/j.neubiorev.2012.03.008.

Fisher, H.E., Brown, L.L., Aron, A., Strong, G., Mashek, D., 2010. Reward, addiction, and emotion regulation systems associated with rejection in love. J. Neurophysiol. 104 (1), 51–60. https://doi.org/10.1152/jn.00784.2009.

Gordon, K.C., Khaddouma, A., Baucom, D.H., Snyder, D.K., 2015. Couple therapy and the treatment of affairs. In: Gurman, A.S., Jacobson, N.S. (Eds.), Clinical Handbook of Couple Therapy, 5th ed. The Guilford Press, New York, pp. 412–444.

Graham, J.W., Olchowski, A.E., Gilreath, T.D., 2007. How many imputations are really needed? Some practical clarifications of multiple imputation theory. Prev. Sci. 8 (3), 206–213. https://doi.org/10.1007/s11121-007-0070-9.

Grezes, J., Berthoz, S., Passingham, R., 2006. Amygdala activation when one is the target of deceit: did he lie to you or to someone else? NeuroImage 30 (2), 601–608.

Gupta, S.K., 2011. Intention-to-treat concept: a review. Perspect. Clin. Res. 2 (3), 109–112. https://doi.org/10.4103/2229-3485.83221.

Hall, J.H., Fincham, F.D., 2006. Relationship dissolution following infidelity: the roles of attributions and forgiveness. J. Soc. Clin. Psychol. 25, 508–522. https://doi.org/10.1521/jscp.2006.25.5.508.

Horowitz, M.J., 1986. Stress-response syndromes: a review of posttraumatic and adjustment disorders. Hops. Community Psychiatry 37 (3), 241–249. https://doi.org/10.1176/ps.37.3.241.

Johnson, S.M., 2019. Attachment Theory in Practice: Emotionally Focused Therapy (EFT) With Individuals, Couples, And Families. Guilford Publications, New York.

Johnson, S.M., Makinen, J.A., Millikin, J.W., 2001. Attachment injuries in couple relationships: a new perspective on impasses in couples therapy. J. Marital. Fam. Ther. 27 (2), 45–155. https://doi.org/10.1111/j.1752-0606.2001.tb01152.x.

Kroger, C., Reisner, T., Vasterling, I., Schutz, K., Kliem, S., 2012. Therapy for couples after an affair: a randomized-controlled trial. Behav. Res. Ther. 50 (12), 786–796. https://doi.org/10.1016/j.brat.2012.09.006.

Laaser, D., Putney, H.L., Bundick, M., Delmonico, D.L., Griffin, E.J., 2017. Posttraumatic growth in relationally betrayed women. J. Marital. Fam. Ther. 43 (3), 435–447. https://doi.org/10.1111/jmft.12211.

Lakens, D., 2013. Calculating and reporting effect sizes to facilitate cumulative science: a practical primer for t-tests and ANOVAs. Front. Psychol. 863 https://doi.org/10.3389/fpsyg.2013.00863.

Lee, J.L., Nader, K., Schiller, D., 2017. An update on memory reconsolidation updating. Trends Cogn. Sci. 21 (7), 531–545. https://doi.org/10.1016/j.tics.2017.04.006.

Lim, C.-S., Kim, J.-I., Kwak, C., Lee, J., Jang, E.H., Oh, J., Kaang, B.-K., 2018. Beta-adrenergic signaling is required for the induction of a labile state during memory reconsolidation. Brain Res. Bull. 141, 50–57. https://doi.org/10.1016/j.brainresbull.2018.04.011.

Lonergan, M., Brunet, A., Rivest-Beauregard, M., Groleau, D., 2021. Is romantic partner betrayal a form of traumatic experience?: a qualitative study. Stress. Health 37, 19–31. https://doi.org/10.1002/smi.2968.

Lonergan, M., Olivera-Figueroa, L.A., Pitman, R.K., Brunet, A., 2013. Propranolol's effects on the consolidation and reconsolidation of long-term emotional memory in healthy participants: a meta-analysis. J. Psychiatry Neurosci. 38 (4), 222–231. https://doi.org/10.1503/jpn.120111.

Lonergan, M., Saumier, D., Tremblay, J., Kieffer, B., Brown, T., Brunet, A., 2016. Reactivating addiction-related memories under propranolol to reduce craving: a

pilot randomized controlled trial. J. Behav. Ther. Exp. Psychiatry 50, 245–249. https://doi.org/10.1016/j.jbtep.2015.09.012.
Maercker, A., Einsle, F., Köllner, V., 2007. Adjustment disorders as stress response syndromes: a new diagnostic concept and its exploration in a medical sample. Psychopathology 40 (3), 135–146. https://doi.org/10.1159/000099290.
Maercker, A., Forstmeier, S., Pielmaier, L., Spangenberg, L., Brähler, E., Glaesmer, H., 2012. Adjustment disorders: prevalence in a representative nationwide survey in Germany. Soc. Psychiatry Psychiatr. Epidemiol. 47 (11), 1745–1752. https://doi.org/10.1007/s00127-012-0493-x.
Maercker, A., Lorenz, L., 2018. Adjustment disorder diagnosis: improving clinical utility. World J. Biol. Psychiatry 19 (sup1), S3–S13. https://doi.org/10.1080/15622975.2018.1449967.
Makinen, J.A., Johnson, S.M., 2006. Resolving attachment injuries in couples using emotionally focused therapy: steps toward forgiveness and reconciliation. J. Consult. Clin. Psychol. 74 (6), 1055–1064. https://doi.org/10.1037/0022-006X.74.6.1055.
Marks, E.H., Franklin, A.R., Zoellner, L.A., 2018. Can't get it out of my mind: a systematic review of predictors of intrusive memories of distressing events. Psychol. Bull. 144 (6), 584–640. https://doi.org/10.1037/bul0000132.
Mattisson, C., Bogren, M., Horstmann, V., 2013. Correspondence between clinical diagnoses of depressive and anxiety disorders and diagnostic screening via the Hopkins Symptom Check List-25 in the Lunby Study. Nord. J. Psychiatry 67 (3), 204–213. https://doi.org/10.3109/08039488.2012.711856.
McGaugh, J.L., 2013. Making lasting memories: remembering the significant. Proc. Natl. Acad. Sci. U. S. A. 110 (sup2), 10402–10407. https://doi.org/10.1073/pnas.1301209110.
Melander, A., 1978. Influence of food on the bioavailability of drugs. Clin. Pharmacokinet. 3 (5), 337–351. https://doi.org/10.2165/00003088-197803050-00001.
Mohr, D.C., Spring, B., Freedland, K.E., Beckner, V., Arean, P., Hollon, S.D., Ockene, J., Kaplan, R., 2009. The selection and design of control conditions for randomized controlled trials of psychological interventions. Psychother. Psychosom. 78 (5), 275–284. https://doi.org/10.1159/000228248.
Monson, C.M., Schnurr, P.P., Stevens, S.P., Guthrie, K.A., 2004. Cognitive–behavioral couple's treatment for posttraumatic stress disorder: initial findings. J. Trauma Stress 17 (4), 341–344. https://doi.org/10.1023/B:JOTS.0000038483.69570.5b.
Mueller, D., Cahill, S.P., 2010. Noradrenergic modulation of extinction learning and exposure therapy. Behav. Brain Res. 208 (1), 1–11. https://doi.org/10.1016/j.bbr.2009.11.025.
Nabbe, P., Le Reste, J.Y., Guillou-Landreat, M., Gatineau, F., Le Floch, B., Montier, T., Van Marwijk, H., Van Royen, P., 2019. The French version of the HSCL-25 has now been validated for use in primary care. PloS one 14 (4), e0214804. https://doi.org/10.1371/journal.pone.0214804.
Nader, K., Schafe, G.E., Le Doux, J.E., 2000. Fear memories require protein synthesis in the amygdala for reconsolidation after retrieval. Nature 406 (6797), 722–726. https://doi.org/10.1038/35021052.
O'Donnell, M.L., Metcalf, O., Watson, L., Phelps, A., Varker, T., 2018. A systematic review of psychological and pharmacological treatments for adjustment disorder in adults. J. Trauma Stress 31 (3), 321–331. https://doi.org/10.1002/jts.22295.
O'Donnell, M.L., Alkemade, N., Creamer, M., McFarlane, A.C., Silove, D., Bryant, R.A., Felmingham, K., Steel, Z., Forbes, D., 2016. A longitudinal study of adjustment disorder after trauma exposure. Am. J. Psychiatry 173 (12), 1231–1238. https://doi.org/10.1176/appi.ajp.2016.16010071.
Pigeon, S., Lonergan, M., Rotondo, O., Pitman, R.K., Brunet, A., 2022. Impairing memory reconsolidation with propranolol in healthy and clinical samples: a meta-analysis. J. Psychiatry Neurosci. 47 (2), E109–E122.
Pitman, R.K., 1989. Post-traumatic stress disorder, hormones, and memory. Biol. Psychiatry 26 (3), 221–223. https://doi.org/10.1016/0006-3223(89)90033-4.
Pitman, R.K., Orr, S.P., Forgue, D.F., de Jong, J.B., Claiborn, J.M., 1987. Psychophysiologic assessment of posttraumatic stress disorder imagery in Vietnam combat veterans. Arch. Gen. Psychiatry 44 (11), 970–975. https://doi.org/10.1001/archpsyc.1987.01800230050009.
Ramsay, C.R., Matowe, L., Grilli, R., Grimshaw, J.M., Thomas, R.E., 2003. Interrupted time series designs in health technology assessment: lessons from two systematic reviews of behavior change strategies. Int. J. Technol. Assess. Health Care 19 (4), 613–623. https://doi.org/10.1017/s0266462303000576.
Rash, C.J., Coffey, S.F., Baschnagel, J.S., Drobes, D.J., Saladin, M.E., 2008. Psychometric properties of the IES-R in traumatized substance dependent individuals with and without PTSD. Addict. Behav. 33 (8), 1039–1047. https://doi.org/10.1016/j.addbeh.2008.04.006.
Roos, L.G., O'Connor, V., Canevello, A., Bennett, J.M., 2019. Posttraumatic stress and psychological health following infidelity in unmarried young adults. Stress Health 35 (4), 468–479. https://doi.org/10.1002/smi.2880.
Sansone, R.A., Sansone, L.A., 2012. Antidepressant adherence: are patients taking their medications? Innov. Clin. Neurosci. 9 (5–6), 41–46.
Sheehan, D.V., 2016. The MINI International Neuropsychiatric Interview v. 7.0.2 for DSM-5.
Soeter, M., Kindt, M., 2015. An abrupt transformation of phobic behavior after a post-retrieval amnesic agent. Biol. Psychiatry 78 (12), 880–886. https://doi.org/10.1016/j.biopsych.2015.04.006.
Steffens, B.A., Rennie, R.L., 2006. The traumatic nature of disclosure for wives of sexual addicts. Sex Addict Compul. 13 (2–3) https://doi.org/10.1080/10720160600870802, 247-26.
Wampold, B.E., 2015. How important are the common factors in psychotherapy?An update. World Psychiatry 14 (3), 270–277. https://doi.org/10.1002/wps.20238.
Weiss, D.S., Marmar, C.R., 1997. The impact of event scale - revised. In: Wilson, J.P., Keane, T.M., Wilson, J.P., Keane, T.M. (Eds.), Assessing Psychological Trauma And PTSD. Guilford Press, New York, NY, US, pp. 399–411.
Whisman, M.A., 2015. Discovery of a partner affair and major depressive episode in a probability sample of married or cohabiting adults. Fam. Process 55 (4), 713–723. https://doi.org/10.1111/famp.12185.
Whisman, M.A., Wagers, T.P., 2005. Assessing relationship betrayals. J. Clin. Psychol. 61, 1383–1391. https://doi.org/10.1002/jclp.20188.
Winokur, A., Winokur, D.F., Rickels, K., Cox, D.S., 1984. Symptoms of emotional distress in a family planning service: stability over a four-week period. Br. J. Psychiatry 144 (4), 395–399. https://doi.org/10.1192/bjp.144.4.395.
World Health Organization, 2018. The ICD-11 Classification of Mental And Behavioural Disorders: Clinical Descriptions And Diagnostic Guidelines. Author, Geneva.
Zelviene, P., Kazlauskas, E., 2018. Adjustment disorder: current perspectives. Neuropsych. Dis. Treat. 14, 375–381. https://doi.org/10.2147/NDT.S121072.