The feasibility and efficacy of incorporating prediction error into reconsolidation therapy with propranolol to treat adjustment disorder stemming from romantic betrayal

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Table of Contents

List of Tables and Figures

List of Appendices

Abstract

Background: Betrayal by a romantic partner can be a shocking experience that results in depression, anxiety, and stressor-related symptoms in the betrayed partner. Adjustment disorder (AD) is a diagnostic construct used to understand the mental health implications that romantic betrayal can have on the impacted partner. While AD can be debilitating, few options currently exist for betrayed individuals who seek treatment outside of the romantic relationship. Although memory reconsolidation impairment with propranolol (i.e., Reconsolidation Therapy; RT) is a promising and innovative treatment for psychiatric disorders stemming from a pathological emotional memory, like AD, animal models and recent evidence among healthy subjects suggests that incorporating a mismatch between what is expected and what actually occurs in therapy may increase the efficacy of RT. **Objectives:** The goal of the current pilot study was to examine the feasibility and efficacy of incorporating mismatch to RT in the treatment of AD. **Method:** Fifteen romantically betrayed participants (aged 18 to 65 years) meeting DSM-5 criteria for AD were randomized to receive 4 to 6 weekly sessions of standard RT, or RT incorporating a mismatch event in the therapy session. Follow-up assessments were conducted 1-week and 3-months post-treatment. Assessment of treatment feasibility was measured by examining participant and clinician protocol adherence (i.e., protocol compliance rates, attendance), as well as protocol acceptability (as measured by the Client Satisfaction Questionnaire) and tolerance by participants (i.e., side effects, retention rates). Efficacy was examined by looking at self-reported symptom reduction pre-and post-treatment across both treatment groups, via the Impact of Event Scale-Revised and the Hopkins Symptom Checklist-25. **Data Analysis:** Feasibility outcomes were analyzed using descriptive statistics, and between-group comparisons were analysed using Fisher's exact tests for categorical variables and

independent *t*-tests for continuous variables. A two-way mixed ANCOVA was conducted to examine preliminary treatment effects, with baseline scores used as a covariate. **Results:** In terms of feasibility, both RT with mismatch and standard RT were well-adhered to by participants and clinicians and were both well-tolerated. Participants who received RT with mismatch ($M = 30.50$, $SD = 2.39$) were more satisfied at post-treatment than those who received standard RT ($M = 26.43$, $SD = 3.51$), $d = 1.38$. In terms of efficacy, no significant time by group interaction was found for stressor-related symptoms or for general psychological distress, even though the between-groups effect size for the change was of moderate magnitude ($d = 0.55$ and $d = 0.52$, respectively). **Discussion:** The incorporation of mismatch into RT was found to be feasible, however preliminary treatment effects did not reveal significant differences between groups. Larger clinical trials examining the implementation of RT with mismatch will be necessary to determine whether this treatment is superior to standard RT. The practical, theoretical and clinical implications of the current findings and future directions for this research are discussed.

Abrégé

Contexte: La trahison amoureuse peut être une expérience bouleversante qui entraîne chez le partenaire trahi des symptômes de dépression et d'anxiété, ainsi que des symptômes de stress. Le trouble de l'adaptation (TA) est un construit diagnostic utilisé pour comprendre les implications sur la santé mentale de la trahison amoureuse chez le partenaire touché. Bien que le TA découlant de la trahison amoureuse puisse être débilitant, il existe peu d'options pour les individus qui recherchent un traitement en dehors du couple. Le blocage de la reconsolidation sous propranolol (i.e., la thérapie de reconsolidation; TR) est un traitement prometteur et innovant utilisé dans les troubles psychiatriques qui découlent d'un souvenir émotionnel intense, comme le TA. Des études récentes chez l'animal et chez le sujet sain suggèrent que l'incorporation d'un certain *mismatch* ou 'décalage' entre ce qui est attendu et ce qui se produit dans la séance de thérapie peut potentialiser l'efficacité de la TR. **Objectifs:** Le but de cette étude pilote était d'examiner la faisabilité d'incorporer du *mismatch* à la TR dans le but d'en améliorer l'efficacité dans le traitement du TA. **Méthode:** Les personnes ayant vécu une trahison amoureuse (âgées de 18 à 65 ans) et qui répondaient aux critères DSM-5 pour un TA ont été randomisées pour recevoir 4 à 6 semaines de TR standard ou de TR avec *mismatch*. Des évaluations ont été effectuées 1 semaine et 3 mois après le traitement. Pour évaluer la faisabilité du traitement, l'adhésion au protocole par les participants et les cliniciens a été évaluée (les taux de conformité au protocole, la présence aux séances), ainsi que l'acceptabilité du protocole de traitement (mesurée via le Questionnaire de satisfaction client) et la tolérance des participants au traitement proposé (les effets secondaires du médicament, le taux de rétention). L'efficacité a été déterminée en examinant les effets de la RT avec *mismatch* par rapport à la TR standard pour réduire les symptômes liés au stress (mesurés avec le *Impact of Event Scale - Revised*) ainsi que

les symptômes de dépression et d'anxiété (mesurés par le *Hopkins Symptom Checklist-25*). **Analyse des données:** les résultats de faisabilité ont été présentés à l'aide de statistiques descriptives et les comparaisons entre les groupes ont été analysées à l'aide du test exact de Fisher pour les variables catégorielles et des tests *t* pour groupes indépendants pour les variables continues. Une ANCOVA mixte à deux facteurs (le groupe et le temps de mesure) a été menée pour examiner les effets préliminaires du traitement sur les symptômes, avec les scores de base utilisées comme covariable. **Résultats:** Les participants et les cliniciens ont bien toléré et ont bien adhéré aux deux types de traitements. Les participants ayant reçu la TR avec *mismatch* (*M* = 30,50, *ÉT* = 2,39) étaient plus satisfaits du traitement que ceux ayant reçu la TR standard (*M* = 26,43, *ÉT* = 3,51), *d* = 1,38. Aucune interaction significative entre le temps et le groupe n'a été trouvée pour les symptômes de stress ou pour la détresse psychologique avec cette taille échantillonnale, même si les tailles d'effet inter-groupes étaient non-négligeables (*d* = 0,55 et *d* = 0,52, respectivement) et allaient dans le sens attendu. **Discussion:** L'incorporation de *mismatch* dans la TR s'est avérée faisable, mais les effets du traitement n'ont pas révélé de différences significatives en terme d'efficacité entre les groupes. De plus grands essais cliniques examinant la mise en œuvre de la TR avec *mismatch* seront nécessaires pour déterminer si ce traitement constitue une amélioration de la TR classique. Les implications pratiques, théoriques et cliniques des résultats actuels et des orientations futures de cette recherche sont discutées.

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Contribution of Authors

This project is part of a larger clinical trial of the treatment of adjustment disorder stemming from romantic betrayal, a protocol implemented in the doctoral work of Michelle Lonergan under the supervision of Dr. Alain Brunet.

Dr. Alain Brunet conceptualized the current study. I helped him devise the mismatch events for the modified treatment used in this project. Additionally, my role was to coordinate the study and manage the team of clinicians, medical doctors, and students involved in various parts of the project, under Dr. Brunet's supervision. I also managed the recruitment, phone screenings, and the data collection, monitoring, and analysis with the help of volunteers who posted recruitment ads, conducted phone screenings, and helped with data entry/checking. Part of the psychological evaluations and all of the treatments were conducted by two psychologists registered with the *Ordre des psychologues de Québec* (OPQ), Drs. Daniel Lavoie and Pascale Everell, as well as Alexandra Bisson-Desrochers and Benjamin Marteau, who were registered with the OPQ as students. Dr. Michelle Lonergan, Dr. Ram Prasad Sapkota and myself further assisted with clinical eligibility and follow-up evaluations under the supervision of Dr. Alain Brunet and Dr. Daniel Saumier. Dr. Pierre Etienne and Dr. Ruben Martins were the study physicians.

Furthermore, I conducted the literature review, analysed and interpreted the statistical results, and wrote the current thesis. Dr. Alain Brunet and Dr. Michelle Lonergan revised the drafts of this thesis and provided advice regarding the statistical analyses.

Chapter I: Introduction

Everyone has or will eventually experience the joy and excitement of a new romantic relationship. Unfortunately, the majority of those relationships will end with intense pain for one or both of the people involved. One of the most common reasons for romantic relationship dissolution is romantic betrayal (Amato & Rogers, 1997; Betzig, 1989; Whisman & Snyder, 2007). The estimated prevalence of infidelity in married couples is 20 to 40%, and this prevalence is slightly higher in cohabiting, unmarried couples (Laumann et al., 2000). While infidelity is a frequently discussed form of romantic betrayal, it is one among other equally harmful and highly common betrayal events, like sudden abandonment or financial deception. For instance, it is estimated that financial infidelity in couples ranges from 13% to 31%, and this rate increases to 41% for couples who combine their finances (Bank, 2017; Goudreau, 2011; National Endowment for Financial Education, 2018; TD Bank, 2020;). Betrayal by one's partner can have a devastating impact on the relationship and the person who was betrayed, leaving the partner with symptoms of depression and anxiety, as well as stressor-related symptoms (Gordon et al., 2004; Turner & Lloyd, 1995; Whisman, 2015).

Romantic betrayal can be devastating for the betrayed partner because it can destroy their expectations of trust and safety in the relationship, as well as their feelings of self-worth and security (Gordon & Baucom, 1998; Johnson et al., 2001). This change in worldviews is similar to the change in views that occurs when one experiences a traumatic event, which destroys one's assumptions of safety and trust in others and the world (Gordon & Baucom, 1998). So like other highly stressful life events, romantic betrayals can lead to the development of a trauma- and stressor-related disorder, notably adjustment disorder (AD), akin to posttraumatic stress disorder (PTSD; American Psychiatric Association [APA], 2013; Lonergan, Saumier, et al., 2020) but

without the life threat. Considering that these individuals report clinically meaningful and enduring stressor-related symptoms, effective treatments are necessary. Unfortunately, few treatments have been found to be effective for AD (O'Donnell et al., 2018).

Reconsolidation therapy (RT) is one treatment option that has been found to effectively treat a number of disorders stemming from a pathological emotional memory, such as PTSD, substance-dependence, specific phobia, and AD (e.g., Brunet et al., 2018; Lonergan et al., 2016; Lonergan, Saumier, et al., 2020; Soeter & Kindt, 2015). RT is based on reconsolidation theory which states that the reactivation of a long-term memory brings it into a labile state during which it is vulnerable to modification (Besnard et al., 2012; Lee, 2009). In view of this theory, the goal of RT is to reduce symptoms that stem from a maladaptive memory by impairing the memory's reconsolidation, most commonly with the administration of the adrenergic beta-blocker propranolol prior to memory reactivation (Agren, 2014; Elsey et al., 2018). Although reconsolidation has been found to be effectively impaired by the administration of propranolol following memory retrieval, some studies have failed to support this finding (e.g., Jobes et al., 2015; Pachas et al., 2015; Wood et al., 2015). The inconsistencies in the literature have been suggested to reflect a failure to apply the appropriate methodology to trigger reconsolidation (see Ecker, 2015). Specifically, pre-clinical evidence from both animal and healthy human research suggest that in order for reconsolidation to be triggered, a prediction error, or a "mismatch" between what is expected to occur and what actually occurs in reality, is necessary (e.g., Pedreira et al., 2004; Sevenster et al., 2013; Soeter & Kindt, 2012). To date, there exists no clinical trial that systematically implements mismatch into RT to test whether the treatment's efficacy for reducing psychiatric symptoms stemming from maladaptive memories can be improved.

The incorporation of mismatch into RT may be a viable avenue for improving this treatment's efficacy to treat AD stemming from romantic betrayal. The current thesis will present the results of a pilot study that addresses this question. The literature review will discuss romantic betrayal in the context of the psychological and neurobiological theoretical frameworks of trauma. The evidence supporting the application of memory reconsolidation impairment for the treatment of the AD stemming from romantic betrayal will then be presented, and this will be followed by a discussion of how reconsolidation-based interventions may be improved with the incorporation of mismatch. Following this literature review will be the method, results, and discussion of a pilot study examining the feasibility of incorporating mismatch into RT to improve its treatment efficacy for AD resulting from romantic betrayal. The thesis will conclude with a discussion of the practical, theoretical and clinical implications of the results.

Chapter II: Review of the Literature

Understanding AD: Diagnosis, prevalence and treatment

Understanding the impact that romantic betrayal can have on the betrayed partner can be facilitated through understanding the diagnostic construct of AD. AD is characterized by the development of emotional or behavioural symptoms (i.e., intrusions, avoidance, anxiety symptoms, and depressive symptoms) in response to a psychosocial stressor and is therefore classified by the *Diagnostic and Statistical Manual for Mental Disorders* (DSM-5) as a trauma- and stressor-related disorder, alongside PTSD (American Psychiatric Association, 2013; Maercker & Lorenz, 2018). While several researchers have argued that romantic betrayal is akin to trauma (e.g., Baucom et al., 2006; Couch et al., 2017; Gordon & Baucom, 1998; Gordon et al., 2004), a traumatic event is defined as an event that involves a life-threat or a threat to one's physical integrity, which is the Criterion A requirement for a diagnosis of PTSD according to the DSM-5 (American Psychiatric Association [APA], 2013). The major difference between trauma and romantic betrayal is that betrayal does not involve such a threat. However, it is often a shocking discovery that results in immense pain in the injured partner and can lead to the development of an AD made up of symptoms related to those experienced by individuals with PTSD (Gordon et al., 2004). These symptoms can be debilitating and can impact the individual's social, emotional, and physical quality of life (Zelviene & Kazlauskas, 2018). For some, these symptoms resolve without treatment 6 months after the stressor is terminated. However, the only study to date that examined the duration of an AD found that the symptoms persisted for up to 2 years for most people (Maercker et al., 2012).

While various forms of betrayal events are common in romantic relationships, the prevalence of AD stemming specifically from romantic betrayal has seldom been investigated.

Still, a number of studies show that participants report depressive and stressor-related symptoms as the result of romantic betrayal (Laaser et al., 2017; Özgün, 2010; Roos et al., 2019; Steffens & Rennie, 2006). In one study that examined the impact of infidelity on the mental health of young adults, it was found that more than half of their sample of 59 undergraduates (51%) met the clinically meaningful cut-off on the Impact of Event Scale-Revised (IES-R), demonstrating significant distress relating to the betrayal (Roos et al., 2019). Similarly, Steffens and Rennie (2006) found that when leaving out Criterion A. of the DSM-IV-TR diagnostic criteria for PTSD, 70% of women who had been romantically betrayed would meet a PTSD diagnosis. Moreover, Whisman (2015) found that the discovery of partner infidelity tended to be associated with a higher prevalence of past year depression. So, although studies that specifically examine the prevalence of a diagnosis of AD resulting from romantic betrayal are limited, a great deal of evidence shows that romantic betrayal leads to clinically meaningful stressor-related symptoms and depressive symptoms, which are characteristic of a diagnosis of AD (APA, 2013; Maercker et al., 2007).

Treatments typically recommended for AD include psychotherapy or the prescription of anti-depressants, however evidence for the efficacy of these treatments for AD is limited and the few existing studies implement low quality methodology (Casey, 2014; O'Donnell et al., 2018). Betrayed partners tend to be given options targeted towards the couple that tend to focus on repairing trust, increasing forgiveness, and/or reducing event-related and marital distress, such as Emotion-focused couple's therapy (Johnson et al., 2001) and the integrative infidelity intervention devised by Gordon et al. (2004). While these treatments have been shown to help couples that struggle with infidelity and other betrayal events, these treatments have not been empirically validated to help individuals outside of the couple context. It is common for couples

to dissolve as the result of betrayal, and effective treatments aimed to help the individuals dealing with their distress in the absence of their partner are necessary (Allen & Atkins, 2012). Further research into treatment options for individuals suffering from AD stemming from romantic betrayal is needed.

Parallels between the psychological effects of romantic betrayal and trauma

The shared psychological impact and symptomatology of PTSD and AD, notably the intrusive thoughts and images, distorted cognitions, hypervigilance, and avoidance, expose an underlying shared etiology among these disorders. Cognitive theories of PTSD can therefore be used to understand AD, as both psychiatric disorders arise from an event that is appraised as a significant threat. Ehlers and Clark (2000) explain that individuals who develop PTSD following a traumatic event interpret the event as ongoing long after it is over, and they view the event as detrimental to their future. Combined with a powerful memory of the traumatic experience (Pitman, 1989), differences in the interpretation of the event are part of what underlies the development of PTSD. This framework may similarly explain how other highly stressful events lead to the development of an AD. For instance, traumatic experiences can shatter core beliefs about others, themselves and the world (Brewin & Holmes, 2003). Gordon et al. (2005) have drawn parallels here between the impact of trauma and betrayal, suggesting that betrayal can have the same impact on some people's beliefs about their partner and relationships more broadly. Cognitive distortions seem to therefore underlie both AD and PTSD.

Adult attachment theory has also been used to understand the impact of romantic betrayal. Attachment theory proposes that humans are inclined to form strong bonds based on interdependence, and betrayal damages this attachment bond (Bowlby, 1969; Hazan & Zeifman, 1999; Johnson et al., 2001). Johnson et al. (2001) have termed this damage to the attachment

bond an “attachment injury” and explain that such an injury often impedes couples’ therapy due to the violation of trust and the experience of this as a trauma. Furthermore, betrayal trauma theory (BTT) has been used to understand the particularly painful experience of traumatic events caused by a loved one. This theory highlights the implications of betrayal trauma which is defined as a threat or violation coming from someone that the betrayed person depends on for survival (Freyd, 1996; Freyd et al., 2007). The literature on BTT mainly focuses on childhood maltreatment, however its tenets have been applied to adolescent and adult romantic relationships as well (Hazan & Shaver, 1987). For instance, BTT posits that individuals who have been betrayed by a loved one may experience “betrayal blindness”, meaning they are fully or partially unaware of the betrayal, which may occur to protect themselves and/or preserve the relationship. Such unawareness parallels the denial that has been reported in qualitative studies involving romantically betrayed adults (Gordon & Baucom, 1998; Lonergan, Brunet, et al., 2020). Overall, while trauma and betrayal events are quite different, it is helpful to understand their similarities by considering the parallels between their psychological impacts. Furthermore, considering that both types of events leave an intensely emotional memory, an understanding of the neurobiology of these memories is necessary for a complete understanding of these disorders.

The neurobiology of AD: Emotional memories and social threat

Unsurprisingly, emotional experiences are better remembered, and the resulting emotional memories are known to be particularly resistant to change and take longer to degrade than non-emotional memories (Pitman, 1989). The stress hormones released in the amygdala when stressful or exciting events occur, such as epinephrine and cortisol, are thought to modulate the consolidation of these memories therefore strengthening them and making them more resistant to later degrading (McGaugh, 2004). It has been proposed that the strengthening of

these emotional memories occurs in order to signal important events worth remembering. While this may be an adaptive process with the role of maintaining important memories, emotional memories from trauma or betrayal are difficult to think about and sometimes become pathological.

Memory consolidation enhancement caused by stress or excitement can become dysregulated during excessively fearful, traumatic events. This dysregulation of the fear response seems to lead to the formation of a strong maladaptive memory that, unlike normal memories, does not lose its emotional salience over time and is too easily reactivated by reminders of the event (McFarlane, 1988; Shalev, 1992; Steil & Ehlers, 2000). These reminders then trigger flashbacks and intrusive thoughts about the event, causing the person a great deal of distress and impairing their ability to function. As emotional memories are strengthened by stress hormones, traumatic memories are thought to have become over-consolidated because of the hyperactivation of the fear response and the excess secretion of norepinephrine (Pitman, 1989). Considering that stressful but non-traumatic events have been found to be associated with similar stressor-related symptoms, this would suggest that the dysregulation of the fear response may not be limited to trauma (Johnson et al., 2001; Lonergan, Saumier, et al., 2020).

Trauma involves the imminent threat of physical harm, to oneself or someone else. Stressful events do not have the same threat of physical pain, but they often involve the threat of social pain, and this is true particularly for romantic betrayal. While physical pain serves the purpose of informing us of actual or threatened tissue damage in our body, social pain informs us of threats to social inclusion as well as potential damage to social bonds (Eisenberger, 2012; Thornhill & Thornhill, 1989). For social animals, social inclusion is necessary for survival and this explains why social pain is processed by the same brain systems as physical pain

(MacDonald & Leary, 2005; Panksepp, 1998). In accordance with this theory, several studies have shown that painful social experiences, such as social rejection, activate similar brain regions as physical pain. For instance, Eisenberger et al. (2003) demonstrated that during a social rejection paradigm in which participants were included and then excluded from a virtual ball-tossing game, participants showed significantly greater activation of the dorsal anterior cingulate cortex (dACC), as well as the anterior insula (AI) which are both involved in the experience of physical pain (Price et al., 1987). Participants in this study who reported greater feelings of rejection also tended to have greater activation in these areas. Kross et al. (2011) demonstrated that physical and social pain stem from similar somatosensory activation by showing that individuals looking at a photo of their ex-partner from a recent painful break-up experienced activation of the dACC and AI, and had similar activation during unpleasant hot stimulation on their forearm. The evidence of shared brain areas for the experience of physical and social pain shed light on why rejection, dissolution of important relationships, and grief over a lost loved one are all experienced as incredibly painful. The threat of experiencing either physical or social pain can therefore equally cause fear and stress for many people.

With an understanding of the shared neural mechanisms underlying physical and social pain, the parallels drawn between the experience of romantic betrayal and trauma become even clearer. Both physical and social threat have the potential to cause a great deal of fear and can both therefore create a pathological memory associated with stressor-related symptoms. Given this shared etiology, individuals who have experienced either of these events may benefit from similar treatments that involve targeting the pathological memory. Lonergan, Saumier, et al. (2020) were the first to propose that the AD stemming from romantic betrayal may benefit from a treatment known to improve symptoms of PTSD, namely Reconsolidation Therapy™ (RT). RT

was developed from the notion that psychiatric symptoms stemming from a pathological emotional memory may be reduced if the salience of that memory is reduced through the impairment of its reconsolidation (see Elsey et al., 2018).

Impairing memory reconsolidation: Neurobiological mechanisms and pre-clinical evidence

Long-term memories were once thought to be permanent once consolidated. In recent decades however, researchers have begun to understand that long-term memories can be updated or weakened through memory reconsolidation, and that this process can be impaired pharmacologically (for reviews see, Besnard et al., 2012; Sara, 2000). Reconsolidation consists of a period following memory reactivation during which previously consolidated memories become vulnerable to modification (Debiec & LeDoux, 2006; Sara, 2000). This process is thought to serve the purpose of naturally maintaining the relevance of memories and contributes to the natural degrading that occurs over time for irrelevant or unimportant memories (Lee, 2009).

Early studies examining interventions that impaired memory reconsolidation included the administration of electroconvulsive shock, protein synthesis inhibitors, or beta-adrenergic blockers to impair the reconsolidation of fear-conditioned memories in animals, and later, similar but less harmful methods were implemented with healthy humans (Misanin et al., 1968; Nader et al., 2000; Przybyslawski & Sara, 1997). These studies typically involve a fear-conditioning paradigm made up of three phases: 1) a conditioning phase during which the subject is trained to fear an otherwise neutral stimulus (e.g., a light, a tone, an image of a spider) through its pairing with an unpleasant stimulus (e.g., a foot shock, a loud noise), 2) memory reactivation of the conditioned response before or after the administration of a pharmacological or behavioural reconsolidation impairing intervention, and 3) a test phase during which the conditioned stimulus

is presented without the unpleasant stimulus and relevant behavioural measures of the fear response are recorded (Schiller & Phelps, 2011).

Studies applying fear-conditioning paradigms have uncovered potential cellular mechanisms involved in memory reconsolidation as well as certain parameters necessary to trigger it (Pedreira & Maldonado, 2003; Sara, 2000). Misanin et al. (1968) conducted the first study that implemented a fear-conditioning paradigm in rats to impair their memory reconsolidation, discovering that electroconvulsive shock could not only impair a fear-conditioned memory that had just been learned but can also impair a fear-conditioned memory 24 hours after it was learned if it was recently reactivated. A later study conducted by Nader et al. (2000) found that administration of the protein-synthesis inhibitor anisomycin also eliminated conditioned fear in rats, but only when its administration was paired with memory reactivation. This study, among others that followed (e.g., Dunbar & Taylor, 2016; Duvarci et al., 2008; Morris et al., 2006), indicated that similar cellular mechanisms such as de novo mRNA protein synthesis play a role in both memory consolidation and reconsolidation. This led to the use of beta-adrenergic blockers, often propranolol, to impair fear-conditioned memory consolidation and reconsolidation in healthy humans (Elsey et al., 2018; Lonergan et al., 2013).

Propranolol has commonly been used to impair memory reconsolidation in healthy human fear-conditioning trials and many studies have found that propranolol paired with memory reactivation effectively attenuates the conditioned fear response in healthy humans compared to a placebo control (see Lonergan et al., 2013 for a meta-analysis). However, some studies have not replicated these findings (Bos et al., 2012, 2014; Chalkia et al., 2019; Tollenaar et al., 2009a, 2009b; Wood et al., 2015). This may be explained by a variety of reactivation parameters, also referred to as boundary conditions, that had not been taken into consideration

during these trials, but that have been suggested to play a role in whether a memory enters reconsolidation, including age of the memory and the availability of new and unexpected information to create a prediction error (see Exton-McGuinness et al., 2014). Indeed, Ecker (2015) highlighted the importance of the presence of a prediction error, or a mismatch between what is expected to occur and what actually occurs, in his review of the literature on reconsolidation impairment. He explained that while a number of studies have indicated the importance of mismatch to trigger memory reconsolidation (e.g., Pedreira et al., 2004; Sevenster et al., 2013, 2014), this parameter was still not implemented in certain studies, all of which were reporting negative results (Bos et al., 2014; Cammarota et al., 2004; Hernandez & Kelley, 2004; Mileusnic et al., 2005; Wood et al., 2015). Mismatch seems to have been a largely overlooked but important parameter to trigger and subsequently impair memory reconsolidation.

Impairing memory reconsolidation as a psychiatric treatment: Clinical evidence

The pre-clinical evidence demonstrating that the salience of fear-conditioned memories could be pharmacologically impaired has been translated into clinical research to ultimately inform the treatment of psychiatric illnesses that stem from a pathological memory. The implications of such a treatment are far-reaching, and this treatment has already been implemented to treat substance-dependence, specific phobia, and trauma- and stressor-related disorders (e.g., Brunet et al., 2018; Lonergan et al., 2016; Lonergan, Saumier, et al., 2020; Soeter & Kindt, 2015). One of the first studies to demonstrate the impairment of memory reconsolidation to treat symptoms in a clinical sample was conducted by Brunet et al. (2008), and demonstrated that administration of post-retrieval propranolol during script-driven imagery of their traumatic event effectively reduced physiological responding in participants suffering from PTSD one week later compared to a placebo control. Following this study, a number of

randomized-controlled trials were conducted to apply this treatment to different populations to explore the scope of benefits that this treatment can have. For instance, several clinical studies of reconsolidation impairment found that cravings in individuals with substance-dependence could be reduced using reconsolidation impairment by reactivating appetitive memories of drug-use (Lonergan et al., 2016; Saladin et al., 2013; Zhao et al., 2011), and others found that symptoms of specific phobia could be improved by pairing propranolol administration with phobia memory reactivation (Soeter & Kindt, 2015).

While there is growing evidence that memory reconsolidation impairment can improve psychiatric symptoms in a number of disorders, there remains no consensus on the most effective procedures for the implementation of this intervention. RT is one treatment based on memory reconsolidation impairment that has been used in a number of studies and has consistently been found to improve trauma- and stressor-related symptoms (Brunet et al., 2011; Brunet et al., 2018; Lonergan, Saumier, et al., 2020). In a recent randomized-controlled trial of RT, involving six weeks of script-driven trauma memory reactivation 1-hour after administration of propranolol, participants suffering from PTSD showed improved clinician-rated and self-reported posttraumatic stress symptoms at post-treatment, and these improvements were maintained over a 6-month follow-up (Brunet et al., 2018). In another recent study by the same team, Lonergan, Saumier, et al. (2020) demonstrated that RT significantly reduced stressor-related symptoms and general psychological distress in a sample of romantically-betrayed participants, compared to a waitlist control. While Lonergan and colleagues found clinically meaningful improvements in over 80% of their participants, 22% still met criteria for a probable diagnosis of AD at post-treatment. So, while RT is an effective protocol for the treatment of psychiatric symptoms including those resulting from betrayal, in light of the literature suggesting the importance of a

prediction error to trigger reconsolidation, this treatment protocol may stand to be improved with the implementation of a mismatch at each of the six treatment sessions.

Evidence for the requirement of mismatch to trigger reconsolidation

In his re-analysis of the literature on reconsolidation impairment, Ecker (2015) explained that the mismatch requirement to trigger memory reconsolidation may explain the conflicting findings across trials of memory reconsolidation impairment. Researchers that inadvertently incorporated mismatch into their protocol may have more effectively triggered reconsolidation, therefore impairing memory reconsolidation more effectively as well. For instance, in fear-conditioning trials involving rats, researchers manipulate the predictability of the reactivation stimulus at the test phase (Besnard et al., 2012; Morris et al., 2006; Pedreira et al., 2004). Besnard et al. (2012) argue that in these paradigms, reconsolidation only occurred when the "predictive context" (i.e., the conditioned stimulus) was terminated and the expected unpleasant stimulus (i.e., the foot shock) was never presented, creating a prediction error.

Considering that memory reconsolidation seems to be an adaptive process that plays the role of updating memories to incorporate new information and facilitate new learning, there would be no reason for long-term memories to undergo reconsolidation if there is no new information to learn (Pedreira et al., 2004). This theory is in line with the Rescorla-Wagner learning model, which posits that learning only occurs when there is new information available (summarized by Lee, 2009; Rescorla & Wagner, 1972). Neurobiological evidence supports this theory as well, as increased or decreased firing of dopamine neurons in the midbrain has been observed when the expected outcome does not match the reality, which is likely what signals to the brain that there is new information to learn (Fernández et al., 2017). Besnard et al. (2012) further explain that if there is low similarity between a previous familiar experience and the

current events, this will lead to an entirely new learning (i.e., extinction), but a high similarity will lead to the updating of the original memory (i.e., reconsolidation), suggesting that for a memory to be modified, the new information must not differ too greatly from what was expected.

While the research on reconsolidation impairment has made major advances in the development of clinical interventions aimed at reducing psychiatric symptoms in a variety of clinical populations, no clinical trial has systematically incorporated mismatch in their procedures. Investigations into a modified RT protocol that incorporates mismatch is therefore warranted. To do so, an important first step is to conduct a pilot study, which can guide the method and design of more extensive clinical trials (Leon et al., 2011).

Current study: Objectives, hypothesis and design

The primary objective of the current study was to examine the feasibility of incorporating mismatch events into RT for the treatment of AD stemming from romantic betrayal and whether the method and procedures are acceptable for potential implementation in a larger clinical trial. To determine this we assessed participant adherence, acceptability, and tolerability of the treatment protocol, as well as clinician adherence to the protocol. The secondary objective was to examine the efficacy of this intervention by examining the preliminary treatment effects of RT with mismatch compared to standard RT. We hypothesized that compared to participants who received standard RT, participants who received RT with mismatch will show greater improvements in self-reported 1) stressor-related, 2) depression and 3) anxiety symptoms at post-treatment and at 3-month follow-up. In addition, differences in post-treatment rates of AD diagnosis based on the DSM-5 diagnostic criteria will be examined to further inform preliminary treatment efficacy.

The current study employs a single-blind randomized-controlled design that includes a screening phase and a 4 to 6-week treatment phase. Post-treatment assessments were conducted 1-week post-treatment and 3 months later. Participants were randomly assigned to receive six weekly sessions of standard RT or RT with mismatch, which both involved the reactivation of the betrayal memory following administration of short-acting propranolol but the reactivation procedure in RT with mismatch included slight variations to the memory reactivation procedures at each session (see Table 1 for a description of the trial design). Recruitment for the study began March 12th 2019, once a No Objection Letter was obtained from Health Canada and approval from the Douglas Research Centre's Institutional Review Board (IRB) was obtained.

Chapter III: Method

Participants

Participants were recruited from the community via posted flyers, online advertisements, and media interviews with the senior researchers. Participants were eligible if they were between the ages of 18 and 65, and had experienced a betrayal or sudden abandonment by a romantic partner whom they were with for at least 6 months prior to the event, and the event had to be currently causing them significant emotional distress as measured by a score of 24 or more on the Impact of Events Scale-Revised (IES-R; Weiss, 2007) and a rating of moderately ill (4 or more) on the Clinical Global Impressions Scale (CGI; Guy, 1976). Participants also had to meet DSM-5 criteria for an AD.

Interested individuals could not participate if they had a systolic blood pressure <100 mm Hg, cardiac rhythm below 55 beats per minute, or a medical condition contraindicating the administration of propranolol (e.g., asthma, chronic cardiovascular illness, diabetes, hypotension). They also could not participate if they had a previous adverse reaction to, or non-compliance with, a beta-blocker, were pregnant or breast feeding, or were taking a medication that could interact with propranolol (e.g., certain anti-depressants, hypertensive medications). Prospective participants were not included in the study if they had a history of substance dependence disorder, bipolar disorder, or psychotic disorder, were participating in another drug trial or had within the past 30 days, or had any other clinical condition that might interfere with the interpretation of the efficacy and safety of the study. In addition, individuals who were evaluated as at significant risk of self-injury or suicidal behavior were considered ineligible to participate in the study and were referred to psychological resources (see Appendix A for the full eligibility criteria).

Procedure

Experimental treatment protocols: Standard RT and RT with mismatch. The study involved two different versions of RT. The original version of RT, or standard RT, involved 4 to 6 weekly treatment sessions consisting of the administration of propranolol followed 1-hour later by memory reactivation using a narrative of the distressing romantic betrayal event (Brunet et al., 2018). Participants were instructed to write the 1-page narrative in the first person, present tense and to incorporate details such as environmental context and physiological sensations they had experienced at the time of the event (see Appendix B). The modified version of RT, or RT with mismatch, involved similar procedures as standard RT, but with the implementation of an element of novelty during each memory reactivation procedure (i.e., a mismatch event; see Table 1) in order to provoke a prediction error and ensure that the memory entered the reconsolidation phase. For both versions of RT, the narrative was solely used to reactivate the memory of the event, and the goal was not to induce abreaction, cognitive reframing, extinction, or insight. The clinician was there to support the participant through the reactivation and if the participant felt overwhelmed at the end of the session, they were guided through relaxation exercises.

Study medication. Participants were administered short-acting oral propranolol per os, which is a synthetic beta-adrenergic blocker known to cross the blood brain barrier and reduce sympathetic activity (O'Carroll et al., 1999; Przybyslawski et al., 1999) known to block consolidation and reconsolidation in animals and humans (Besnard et al., 2012). The dose of the medication was set at 1mg/kg of body weight, not exceeding a dose of 80mg.

Clinician background. The study clinicians were psychologists or students who were in the process of completing their clinical training, all of whom were registered with the *Ordre des Psychologues du Québec* (OPQ). All study clinicians completed the three-day RT training

devised and taught by Dr. Alain Brunet (see www.reconsolidationtherapy.com). Furthermore, clinicians observed sessions of standard RT and RT with mismatch conducted by senior clinicians prior to offering the therapy themselves. A homemade adherence measure based on the RT treatment manual was used to ensure quality of the intervention (Brunet & Lonergan, unpublished manual).

Eligibility assessment. Individuals deemed eligible based on a brief phone screening were invited for a comprehensive psychological and medical evaluation at the Douglas Mental Health University Institute, in Verdun QC, Canada. During the evaluation session, candidate participants were first explained the research project in detail, as well as their rights as a participant in the study. They were explained that they could withdraw from the study at any time without consequences to themselves. If they agreed, they were asked to sign the consent form. Once the consent form was signed, participants provided socio-demographic information. They were then administered the Mini International Neuropsychiatric Interview for the DSM-IV (MINI-S; Lecrubier et al., 1997) in order to determine eligibility to further participate in the study by ruling out the presence of major psychiatric comorbidities and to determine whether AD diagnostic criteria was met (see Appendix A for full eligibility criteria). Participants were then asked to fill out assessment questionnaires. Upon completion of the questionnaires, participants were brought to the medical doctor's office and they underwent a non-invasive medical evaluation with a medical doctor. Participants who were found to be eligible were prescribed 6 doses of propranolol (1mg/kg) by the doctor, but not exceeding an 80mg dose. Those who were not deemed eligible were thanked and were referred to community resources. Eligible participants were placed on a 4-week waiting list and received questionnaires to fill out mid-way through.

Procedures for the treatment sessions. Following the 4-week waiting list, participants were invited to the Douglas for the first treatment session. During the first session, participants were administered the first dose of propranolol. Their heart rate and blood pressure were monitored at the beginning of the first session and once every half hour for 60 minutes. Participants were given the remaining five doses of propranolol to bring home and were explained to take these doses 1-hour before the beginning of the subsequent treatment sessions. They were then asked about their symptoms during the previous week and were administered questionnaires. After they completed the questionnaires, the participants were asked to write the narrative of their betrayal event. If the participant had experienced several romantic betrayal events, they were told to write the narrative with a focus on the event that continues to cause them the most intense psychological and emotional distress. Once finished, they were asked to read the narrative aloud to the experimenter. Following the memory reactivation procedure, the clinician asked how that experience was for the participant, and which parts were the most difficult for them to read. When the participant was ready, the experimenter ended the session.

After the first treatment session, participants were randomized to either receive standard RT or RT with mismatch using permuted block randomization with a block size of 4, stratified by gender and betrayal event type (infidelity vs. other) with a 1:1 allocation ratio. As is always the case in psychotherapy research, participants and clinicians could not be blind to group allocation due to the different procedures implemented in each treatment. However, post-treatment and follow-up assessments were conducted by third parties who were blind to group allocation.

Before the subsequent treatment sessions (treatments 2 to 6), participants were reminded to take the propranolol at home 1 hour prior to the treatment session with a small snack. During

these sessions, the participants read the narrative aloud to the experimenter, who had previously transcribed the narrative. Participants randomized to receive RT with mismatch were presented with an element of novelty at each treatment session with the goal of inducing a prediction error and to therefore ensure that reconsolidation was being triggered consistently throughout the treatment. The mismatch events are described in Table 1.

Follow-up assessments. Two follow-up assessments were conducted post-treatment. The first follow-up took place one week following the last treatment visit, while the other was scheduled 3 months later. At each follow-up assessment, participants were administered the MINI (Lecrubier et al., 1997) and participants were administered the self-report questionnaires.

Outcome measures for study feasibility

Protocol adherence, acceptability, and tolerability by participants. In order to determine the feasibility of RT with mismatch, the adherence, acceptability, and tolerability of the treatment protocol by the participants will be evaluated. Protocol adherence by participants was defined by the extent to which participants followed the procedures as directed by the clinician and research team. Specifically, the rate of inconsistencies in attendance, propranolol compliance issues, and memory reactivation procedure compliance issues were evaluated. Based on the results of a recent open-label trial offering standard RT to individuals with AD stemming from romantic betrayal (Lonergan, Saumier, et al., 2020), we determined that a rate of 15% or less of these deviations indicates adequate protocol adherence by participants. The rates were calculated by dividing the observed rates of non-compliance over the total number of possible instances of non-compliance (i.e., for each participant, at each treatment session, and for each outcome assessed). To inform protocol tolerability by participants, the rate of side effects to propranolol as well as the retention rates throughout the treatment phase were examined. The

expected retention rates in this population are 80%, based on the work by Lonergan, Saumier, et al. (2020) as well as the average drop-out rate of about 18% in clinical trials for PTSD treatments (Imel et al., 2013). Participant's treatment acceptability was determined by the participant's satisfaction post-treatment, as assessed by a self-report satisfaction questionnaire.

Protocol adherence by clinicians. The ease with which the study method and treatment procedures were implemented will be determined by how closely the protocol was followed by the research team. Specifically, if the rate of protocol deviations was found to be 10% or less, the procedures were considered to have been adequately implemented. For the protocol of RT with mismatch, failure to administer the mismatch events at the correct treatment session was considered a protocol deviation. For the protocol of standard RT, the implementation of any mismatch event was considered a protocol deviation. For both protocols, if the reactivation narratives were longer than 1-page typed, and were not written in the first person, present tense, this was considered a protocol deviation. As for participant compliance rates, clinician protocol adherence rates were calculated by dividing the observed rates of protocol deviations over the total number of possible instances of deviations (i.e., for each participant, at each treatment session, and for each outcome assessed).

Outcome measures for treatment efficacy

Treatment efficacy was evaluated with an examination of pre-post effect sizes and an analysis of preliminary treatment effects between those who received standard RT and those who received RT with mismatch using two main outcomes: stressor-related symptoms as measured by the Impact of Event Scale-Revised (IES-R; Weiss, 2007) and general psychological distress as measured by the Hopkins Symptom Checklist (HSCL-25; Winokur et al., 1984).

Psychometric properties of assessment measures for screening and outcome assessments

Assessment measures for the in-take and follow-up evaluations. The Mini International Neuropsychiatric Interview (MINI; Lecrubier et al., 1997) is a brief clinician-rated, semi-structured interview for the DSM-IV that was used to confirm AD diagnosis at the intake assessment, and at the 1-week and 3-month follow-up evaluations. The MINI was also used to assess potential comorbidities, such as major depressive disorder, panic disorder, PTSD, generalized anxiety disorder, social anxiety disorder, alcohol or drug dependence disorder. In addition, the Clinical Global Impression Scale (CGI; Guy, 1976), a clinician-rated measure of symptom severity and improvement, was administered at in-take, after each treatment session, at post-treatment and 3-month follow-up.

Assessment measure for study feasibility. The Client Satisfaction Survey (CSQ-8; Larsen et al., 1979) was administered at the last treatment visit (Visit 6) to determine participant satisfaction with the treatment. The questionnaire consists of questions regarding participants' impression of their improvement and of the quality of the treatment they received. The CSQ-8 is a valid and reliable questionnaire with a Cronbach's alpha of 0.93, indicating a high internal consistency (Larsen et al., 1979).

Assessment measures for treatment efficacy. The Impact of Event Scale-Revised (IES-R; Weiss, 2007) was administered at every visit to measure the severity of stressor-related symptoms over the past week. The IES-R is a self-report measure made up of 22 items from the three PTSD symptoms clusters: 7 items for intrusions, 8 items for avoidance, and 7 items for hyperarousal. The items are scored on a 5-point Likert scale, ranging from 0 (Not at all) to 4 (Extremely). The scores are summed to obtain subscale and total severity scores, with a clinical cut-off of 33. The IES-R is known to be a reliable and valid measure, with good test-retest

reliability (r = 0.89 to 0.94) and internal consistency for the subscales ranging from 0.79 to 0.97 (Creamer et al 2003).

In order to assess general psychological distress, the Hopkins Symptom Checklist (HSCL-25; Winokur et al., 1984) was administered at every visit. The HSCL-25 is a self-report questionnaire, abbreviated from the Symptom Checklist-90, which measures general psychological distress over the previous week. The HSCL consists of 25 items scored on a 5-point Likert scale (1 = Not at all, 5 = Extremely), with 10-items that evaluate symptoms of anxiety and 15 that evaluate symptoms of depression, and the clinical cut-off is 1.75. The HSCL-25 is a reliable and valid measure of general psychological distress, with a Cronbach's alpha of 0.89 for the depression subscale, 0.87 for the anxiety subscale, and 0.93 for the overall scale (Nabbe et al., 2019).

Statistical analyses

Evaluating study feasibility. In order to assess the primary outcomes of protocol adherence, acceptability, and tolerability, outcomes relating to the procedures such as retention rates and protocol deviations were described as percentages. Fisher's exact tests were conducted on categorical variables to determine whether these variables are associated with either group. To compare participant satisfaction, between-group effect sizes and confidence intervals for CSQ scores were examined. Additionally, sociodemographic and clinical characteristics of the groups were reported and compared with independent sample's t-tests as a preliminary measure to assure that the randomization procedures appropriately balanced participant characteristics across the groups.

Evaluating treatment efficacy. To examine the preliminary treatment effects of incorporating mismatch into RT, between-group and within-group effect sizes and confidence

intervals were calculated to examine change in symptom severity on the IES-R and the HSCL-25 from pre- to post-treatment between groups. As previously recommended for pilot studies which are by nature underpowered to detect a significant effect (Lee et al., 2014), 75%, and 95% confidence intervals are reported to demonstrate trends in the data and inform larger scale trials. In addition, a series of two-way mixed analyses of covariance (ANCOVA) were conducted on change in IES-R and HSCL-25 scores between groups from the second session (i.e., the effect of one treatment) to post-treatment, with scores from the first session entered as a covariate. Treatment group was the between-subjects factor and time was the within-subjects factor. Analyses were two-sided, with an alpha level of .05. Normality was assessed for all data distributions using the Shapiro-Wilks test. If normality is violated, the appropriate non-parametric tests will be conducted. Furthermore, effect sizes and confidence intervals as well as Fisher's exact tests were conducted on post-treatment and follow-up rates of AD diagnoses to explore preliminary between-group differences in the diagnoses. All analyses were conducted using SPSS v. 26.

Chapter IV: Results

The participant flow-chart is depicted in Figure 1. Of 28 participants who were assessed for eligibility, 17 participants were included in the study. Two participants dropped out while on the waiting list; one no longer wanted to participate and the other had a change in medical eligibility. The final study sample was therefore comprised of 15 participants; eight were randomized to receive RT with mismatch and seven were randomized to receive standard RT. Sociodemographic information for the final sample is presented in Table 2. Moreover, 13 participants completed six treatments, two participants completed five treatments, and eight participants completed the follow-up assessment. The average amount of time between the 1-week post-treatment assessment and follow-up assessment was 4.63 months (*SD* = 2.82). Of the seven participants who did not complete the follow-up, three participants were lost to follow-up without providing a reason, while the follow-up for the remaining four participants had not yet occurred during the writing of this thesis. Descriptive results for the follow-up evaluation are reported in Table 3.

Between-group differences in continuous baseline characteristics were compared using independent sample's Student's *t*-tests as a preliminary assessment of whether the randomization procedures evenly distributed these characteristics. In addition, differences in categorical baseline characteristics were compared using Fisher's exact tests (see Table 2 for demographic characteristics of the sample). As for psychiatric comorbidity in the sample (as assessed by the MIN; Lecrubier et al., 1997), 8/15 (53.3%) of the participants met criteria for past depression and 3/15 (20%) met criteria for an isolated past depressive episode. Furthermore, 3/15 (20%) participants met criteria for an anxiety disorder (social phobia, generalized anxiety disorder,

panic disorder). Fisher's exact tests revealed no significant between-group differences in psychiatric comorbidity (all *p*'s > .05).

Study feasibility: Protocol adherence, acceptability, and tolerability by participants.

The rate of inconsistencies in attendance was used to assess adherence to the treatment protocol and was determined by the number of sessions that were missed and/or rescheduled by participants, with a rate of 15% or more considered to be non-compliant. The rate of inconsistencies in attendance was 6.3% in the mismatch group (three participants missed 1/6 sessions) and 4.8% in the standard group (two participants missed 1/6 sessions). As for propranolol compliance, one participant in the mismatch group forgot once to take the propranolol 1-hour before the treatment session and the session had to be rescheduled. No other participant forgot to take their propranolol before a session, and all participants took the correct dose of the medication. The rate of propranolol non-compliance was therefore 2.1% in the mismatch group and 0% in the standard group. One participant in the standard group did not engage in memory reactivation procedures at their 5th treatment session, as they found it too difficult to talk about their event. The rate of memory reactivation protocol non-adherence was therefore 2.4% in the standard group and 0% in the mismatch group. To assess protocol acceptability, between-group effect sizes and confidence intervals were examined to determine whether differences exist in post-treatment satisfaction between the groups. Participants in the mismatch group (M = 30.50, SD = 2.39) reported more satisfaction with the treatment than those in the standard group (M = 26.43, SD = 3.51), with a moderate effect size observed in favour of RT with mismatch (d = 1.38; 95% CI = -7.38 – -0.77).

Treatment tolerability was determined by the retention rates (see Figure 1) and the side effects in each group. In both groups, all participants completed five to six treatment sessions. In both treatment groups, no participant experienced severe side effects from the medication. However, in the mismatch group, 5/8 participants experienced mild side effects (i.e., numbness, stomach pains, dizziness, difficulty concentrating, fatigue). In the standard group, 3/7 participants experienced mild side effects (i.e., nausea, fatigue, numbness, dizziness, diarrhea). Most side effects were found after a single session, dissipated within a few hours, and did not recur. The only side effects found to recur at several treatment sessions were fatigue (n = 1) and muscle numbness (n = 3). Three participants (mismatch n = 2, standard n = 1) experienced these side effects at more than one session. No participant dropped out as the result of a side effect. Overall, both protocols have been very well-tolerated by the participants.

Study feasibility: Protocol adherence by clinicians

Protocol deviations by clinicians, including administration of mismatch events at the wrong session (see Table 1 for the appropriate mismatch events by session), administration of mismatch events to participants in the standard group, and quality of the memory reactivation narratives, were assessed to determine the clinicians' protocol adherence. Three participants from the standard group and one participant from the mismatch group had to complete treatment sessions via online videoconference due to the physical distancing measures imposed by the COVID-19 pandemic. While two participants in the standard group received all six treatments via videoconference, two participants received only their final one or two sessions via videoconference. The change from in-person to online treatment that these two participants experienced may constitute a mismatch and is therefore considered a protocol deviation. Furthermore, in the standard group, two participants had a change of clinician during the

treatment due to scheduling difficulties. For all participants in the mismatch group excluding the one who received a videoconference session constituting an additional mismatch event, all mismatch events were administered at the correct treatment sessions. In sum, there were 3/42 (7.1%) deviations in standard group and 1/48 (2.1%) deviations in the mismatch group. As for the betrayal narratives, the texts were required to be 1-page typed, and written in the first person, present tense. One participant in each group had narratives that were longer than a single page typed, and one participant in the mismatch group wrote their script in the wrong (past) tense. The overall rate of deviations by clinicians was 4/56 (7.1%) for the standard group and 3/64 for the mismatch group (4.7%). Considering that there are fewer than 10% protocol deviations by clinicians, both treatment protocols are considered to have been well-adhered to.

Preliminary treatment efficacy of incorporating mismatch

Changes in overall stressor-related symptoms (IES-R). Means, standard deviations, and within-group effect sizes for the IES-R for each group over time are presented in Table 3. Visual inspection of the mean change in stressor-related symptoms from baseline to post-treatment in the mismatch group compared to the standard group shows a moderate between-group effect size on mean change scores from pre- to post-treatment of $d = 0.55$ with a trend toward an effect in favour of RT with mismatch (95% CI = -32.98 – 11.23; 75% CI = -23.20 – 1.45). Both groups reported stressor-related symptoms below the clinically meaningful cut-off of 33 (Creamer et al., 2003) at post-treatment.

Exploring the intrusion, avoidance, and hypervigilance subscales of the IES-R. Table 4 depicts the means, standard deviations, and within-group effect sizes for the intrusion, avoidance, and hypervigilance subscales of the IES-R. Visual inspection of the mean change in symptom severity for each subscale of the IES-R revealed moderate effect sizes showing greater improvement in intrusions ($d = 0.71$; 95% CI = -9.26 – 0.47; 75% CI = -8.22 – -0.57) and

hypervigilance (d = 0.64; 95% CI = -10.91 – 1.12; 75% CI = -9.63 – -0.16) with a trend in favour of RT with mismatch, but improvement in avoidance symptoms was similar between-groups (d = 0.17; 95% CI = -8.93 – 5.75; 75% CI = -7.37 – 4.19).

Results from a series of mixed ANCOVAs on the IES-R. A two-way mixed ANCOVA was conducted on IES-R total scores, with treatment group as the between-subjects factor and time as the within-subjects factor and with baseline IES-R scores as a covariate (i.e., the first session). All assumptions (homoscedasticity, homogeneity of variances, and homogeneity of regression slopes) for the mixed ANCOVA were met. The ANCOVA revealed no main effect of group, $F(1, 12) = 0.38$, $p = .550$, or time, $F(1, 12) = 1.43$, $p = .260$. The time by group interaction was not significant ($F[1, 12] = 2.53$, $p = .140$; see Figure 2). Furthermore, a series of two-way (time x group) mixed ANCOVAs were conducted to explore the preliminary treatment effects on the IES-R subscales, with baseline scores as a covariate. There were no significant main effects of time for intrusion, $F(1, 12) = .10$, $p = .757$, avoidance, $F(1, 12) = .54$, $p = .478$, or hypervigilance, $F(1, 12) = .55$, $p = .473$. In addition, there were no significant main effects of group for intrusions, $F(1, 12) = .002$, $p = .961$, avoidance, $F(1, 12) = 1.99$, $p = .184$) or hypervigilance, $F(1, 12) = .01$, $p = .928$). Furthermore, the time by group interaction was not significant for any of these subscales (intrusion: $F(1, 12) = 4.19$, $p = .063$, avoidance: $F(1, 12) = 1.29$, $p = .279$, hypervigilance: $F(1, 12) = 1.23$, $p = .289$).

Changes in overall general psychological distress (HSCL-25). Means, standard deviations, and within-group effect sizes for the HSCL-25 for each group over time are presented in Table 3. Visual inspection of mean pre-post change in HSCL-25 scores revealed a trend toward greater improvement in symptom scores for participants who received RT with mismatch (d = 0.52; 95% CI = -0.81 – 0.17; 75% CI = -0.70 – 0.07). Both groups reported general

psychological distress symptoms below the clinically meaningful cut-off of 1.75 at post-treatment (Nabbe et al., 2019).

Exploring the anxiety and depression subscales of the HSCL-25. Table 4 depicts the means, standard deviations, and effect sizes for the depression and anxiety subscales of the HSCL-25. Visual inspection of the mean change for each subscale revealed similar improvement between groups on the anxiety subscale (d = 0.11; 95% CI = -0.51 – 0.38; 75% CI = -0.41 – 0.29) and a trend toward greater improvement in depressive symptoms in favour of RT with mismatch (d = 0.57; 95% CI = - 1.05 – 0.18; 75% CI = -0.92 – 0.04).

Results from a series of mixed ANCOVAs on the HSCL-25. A two-way (time x group) mixed ANCOVA was conducted on mean HSCL-25 scores, with baseline HSCL-25 scores included in the model as a covariate (see Figure 3). The a priori assumptions for the mixed ANCOVA were met. The analysis revealed no main effect of group, $F(1, 12) = 0.06$, $p = .810$, or time, $F(1, 12) = 1.147$, $p = .305$. The ANCOVA did not reveal a significant interaction between treatment group and time, $F(1, 12) = 0.37$, $p = .555$. In addition, a series of two-way (time x group) mixed ANCOVAs were conducted to explore the HSCL-25 subscales (depression and anxiety), with baseline scores as a covariate. There were no significant main effects of time for the anxiety, $F(1, 12) = 0.56$, $p = .470$, or depression subscales, $F(1, 12) = 1.86$, $p = .197$, nor were there any significant main effects of group for the anxiety, $F(1, 12) = 0.001$, $p = .978$, or depression subscales, $F(1, 12) = 0.05$, $p = .832$. Analysis of the HSCL-25 subscales revealed no significant interaction between group and time on anxiety, $F(1, 12) = 0.03$, $p = .876$, or depression scores, $F(1, 12) = 0.52$, $p = .487$.

Changes in rates of AD at post-treatment. Change in AD diagnosis at post-treatment was assessed using the MINI-S AD diagnostic module. At post-treatment, two participants

(mismatch $n = 1$, standard $n = 1$) still met criteria for an AD. The Fisher's test revealed no difference on post-treatment AD diagnosis between groups ($p > .05$).

Descriptive results and feasibility of the follow-up evaluation.

Of the 11 participants who were invited for the 3-month follow-up, eight (72.7%) responded and completed the evaluation (standard $n = 3$, mismatch $n = 5$). Tables 3 and 4 show mean IES-R and HSCL-25 scores at the follow-up evaluation. Both groups continued to report IES-R scores below the clinical cut-off of 33 on the IES-R. Although both groups reported low general psychological distress at follow-up, the mismatch group obtained HSCL-25 scores slightly above the clinical cut-off of 1.75. No participant who returned to follow-up met diagnostic criteria for an AD.

Chapter V: Discussion

The current study was the first to assess the feasibility and preliminary efficacy of incorporating mismatch into RT to treat the AD stemming from romantic betrayal. Considering the evidence from pre-clinical fear-conditioning studies demonstrating the importance of mismatch to trigger memory destabilization and subsequently, reconsolidation, an understanding of the feasibility of incorporating this phenomenon into a treatment protocol and its preliminary treatment effects is the logical next step. This study therefore bridges an important gap in the literature suggesting that mismatch in reconsolidation impairment may at least partially explain the mixed results concerning the efficacy of RT. Furthermore, given that effective treatments for romantically betrayed individuals suffering from an AD are scarce, the current study sheds light on a viable treatment option for this population that would provide them with the opportunity to receive treatment outside of their relationship, and that is directly relevant to the betrayal they experienced.

The findings of the current study provide support for the feasibility of implementing mismatch into RT to treat the AD stemming from romantic betrayal. The between-group effect sizes on pre-post change scores were moderate and in the expected direction for both stressor-related symptoms and general psychological distress, thus providing important information for planning sample sizes in future large scale randomized controlled trails. The following provides a summary and discussion of the current results as well as a discussion of the implications of these findings for future clinical trials and for clinical practice.

Study feasibility: Adherence, tolerance, and acceptance by participants

In both protocols, there were fewer than 15% non-compliance issues with the memory reactivation procedures, propranolol administration, and attendance in either group. In each

group, there was only a single instance of non-adherence to the propranolol or memory reactivation procedures, and attendance was good in both groups. The memory reactivation and propranolol administration protocols used in this study were therefore well-adhered to by participants, even when mismatch was incorporated, suggesting that the current mismatch protocol is suitable for further use in research and clinical practice. When examining participants' satisfaction with the two treatment protocols, as measured by their scores on the CSQ, participants who received mismatch RT were more satisfied than those in the standard RT. Finally, both treatments were found to be well-tolerated by participants, as they showed minimal side effects, and there were no dropouts during the treatment. The experience of side effects was not expected to differ between the groups because all participants received 1mg/kg of propranolol. However, in order to demonstrate the feasibility of offering RT with mismatch, a discussion of the side effects is relevant. The side effects found in the current sample are in line with the typical side effects reported by individuals who take propranolol for other health reasons (i.e., hypertension, migraines, anxiety; Prichard & Gillam, 1964; Weber & Reinmuth, 1972). Participants in both groups took a minimal dose of propranolol compared to people who take the medication daily, so the risk of side effects was minimal, which is reflected in the current findings.

Study feasibility: Protocol adherence by clinicians

Both treatment protocols were well-adhered to by the clinicians, who did not commit more than 10% of protocol deviations in either protocol. Importantly, the COVID-19 global pandemic was declared while the treatment phase was ongoing, and several treatment sessions had to be administered in a videoconferencing platform. Because of this, one participant from the standard group and one participant from the mismatch group had a change in treatment format

while their treatment was ongoing. Nevertheless, the occurrence of deviations by clinicians was minor, suggesting that both treatment protocols were easy to implement. These results suggest that implementing the current mismatch protocol does not complicate the ease of providing RT. However, it is important to note that the current mismatch treatment protocol was devised for a research setting, and feasibility should be further investigated in clinical settings.

Treatment efficacy: Preliminary treatment effects of RT with mismatch vs standard RT

Preliminary treatment effects demonstrate greater symptom improvement for the RT with mismatch group compared to the those who received standard RT, as evidenced by moderate between-group effect sizes on pre to post treatment improvement with a trend in favour of RT with mismatch for both stressor-related symptoms (IES-R) and general psychological distress (HSCL-25), particularly for intrusions, hypervigilance, and depressive symptoms. An a priori power analysis suggests that a sample size of $n = 54$ participants per group (a total sample of $n = 108$ participants) would be necessary to achieve 80% statistical power and an alpha level of .05 in a larger scale version of the current study with an estimated effect of $d = 0.55$. Larger clinical trials with greater statistical power are therefore the next necessary step to investigate the effectiveness of incorporating mismatch into RT.

At post-treatment, a minority of participants (mismatch $n = 1$, standard $n = 1$) met DSM-5 criteria for an AD. This suggests that both treatments improved symptoms of AD, replicating the findings of Lonergan, Saumier, et al. (2020) for standard RT. Of the 11 participants whose 3-month follow-up was reached before the writing of this thesis, 72.7% responded, a rate which matched the follow-up response rate of Lonergan, Saumier, and colleagues (2020) who had a 71.4% response rate at a 4-month follow-up. Stressor-related symptoms and general psychological distress increased slightly in the mismatch group at follow-up, but remained below

the clinically meaningful cut-off for the IES-R. The sample of participants who responded to the follow-up was small, however the small increase in symptoms for the mismatch group may indicate a need to modify the mismatch protocol implemented in the study.

Limitations

Firstly, while participants who received RT with mismatch reported higher satisfaction with the treatment, this may be explained by the fact that participants could not be blinded to their group allocation and they therefore knew whether they were receiving the modified or standard version of RT. Their scores on the CSQ may reflect an expectation that the modified treatment was better. Furthermore, considering that the RT with mismatch protocol involved tasks that have been argued to promote distancing from the event and closure (i.e., reading the narrative in the third person, past tense, see Crawley, 2010), participants who received RT with mismatch may have felt more closure at the end of the treatment than those in the standard group and this may have influenced their satisfaction post-treatment. Thus, although RT incorporated with mismatch appears to be associated with higher treatment satisfaction, this difference should be interpreted considering these potential confounds. Furthermore, the current sample was made up of mostly Caucasian, heterosexual individuals with a high income, and this may limit the generalizability of the current findings to individuals of other cultures, sexual orientations, or socio-economic statuses. These groups may experience romantic betrayal differently or they may have differing beliefs relating to romantic betrayal and monogamy, which may play a role in their treatment outcomes. Moreover, more than half of the sample was no longer in the relationship when they participated in the study. Treatment outcomes may differ for individuals who are still in a relationship with the offending partner, especially if the betrayal is ongoing. Future research that includes more diversity in their sample is necessary in order to determine

whether RT with mismatch is feasible and effective for these individuals with differing backgrounds and who may still be in a relationship with the offering partner.

Future directions

What constitutes mismatch for long-standing maladaptive memories? No other clinical trial to date has systematically implemented mismatch within a reconsolidation-based treatment protocol and considering the current lack of knowledge regarding the translation of mismatch to clinical practice, continued research into this phenomenon is necessary to improve reconsolidation-based interventions. Previous work on mismatch in humans is limited to experimental fear-conditioning paradigms, which incorporate mismatch by using a modification of the predictability of the reactivation stimulus during the test phase (Besnard et al., 2012; Morris et al., 2006; Pedreira et al., 2004). For instance, in pre-clinical research on reconsolidation impairment, 24 hours after an unconditioned stimulus (e.g., shock) is conditioned to a tone, the conditioned memory is reactivated by presenting the tone without the subsequent stimulus, in order to measure the conditioned fear response. Presentation of the conditioned stimulus without the unconditioned stimulus contradicts the participant's expectation, creating a prediction error and triggering memory destabilization and subsequently, reconsolidation (Ecker, 2015; Pedreira, 2004; Exton-McGuinness et al., 2015). Here, incorporating a prediction error is rather straightforward, in that the fear-conditioning paradigm can be manipulated to include the presence or absence of the unconditioned fearful stimulus (e.g., shock) following the presentation of the conditioned stimulus, which directly violates the subject's expectations. On the other hand, when working with idiosyncratic memories of life events, the memory of the fear-inducing situation has long been formed and it may be more complex to create a prediction error that adequately challenges a participant's expectations enough to trigger memory

destabilization of the particular maladaptive memory. Insight into the types of mismatch events that can trigger reconsolidation of emotional autobiographical memories is necessary.

Boundary condition between extinction and reconsolidation. Mismatch is part of learning in every aspect of life, is vital to induce memory updating, and serves several purposes. When mismatch, or prediction-error, is large, memory reconsolidation is not triggered, but rather, the consolidation of a new extinction memory takes place that competes with the older memory. This has been referred to as a boundary condition on reconsolidation (Exton-McGuinness et al., 2015; Sevenster et al., 2014), and may at least partially explain why reconsolidation-based psychiatric interventions work better for some individuals than others. The current study provides a preliminary attempt at implementing mismatch events that can trigger memory destabilization and reconsolidation processes, rather than extinction learning, however this boundary was not explicitly assessed. Future studies should consider studying the variability in mismatch events that can lead to reconsolidation or extinction. For instance, researchers may consider comparing several mismatch procedures that vary in terms of their level of prediction-error to a no-mismatch control group, to determine which methods are most effective at reducing emotional memory responses. Such investigations will help the development of standardized and effective mismatch events to incorporate into clinical intervention protocols in larger randomized controlled trials.

Individual differences and relevant mismatch events. The mismatch protocol used in the current study was purposefully designed to flexibly apply to a wide range of memories, as to reactivate and create a prediction error for all participants regardless of their betrayal event. However, another boundary condition for reconsolidation is that the new information must be relevant to the memory in question, and specifically involve new information to integrate into the

old memory (see Exton-McGuinness et al., 2015). In private practice, it may therefore be beneficial for clinicians to determine mismatch events prior to each session so that they are more relevant to the client's betrayal experience. For example, for someone that experienced a sudden abandonment and could no longer communicate with their ex-partner, having the participant write a final letter detailing their experience of the betrayal directed to their ex-partner may constitute a more idiosyncratic mismatch event. Providing mismatch events that are relevant to the specific betrayal such as this may create a stronger mismatch, ensuring the memory enters reconsolidation.

Therapy offered via telecommunication: The adaptability of RT with mismatch. During the current study, a global pandemic was declared due to COVID-19. While this resulted in briefly putting the current study on hold, once ethics approval was obtained to continue the ongoing treatments via videoconference, it was relatively simple to transfer the treatments to an online format using the teleconferencing platform Zoom. This adjustment sheds light on the importance of developing accessible and easy to administer psychiatric treatments, like RT. Overall, both standard RT and RT with mismatch were transferred to an online format in the current study for a small number of participants, and the feasibility results do not seem to have been impacted by this change. While the current study did not assess the feasibility of implementing RT with and without mismatch online, they indicate that such a transition is possible and may in fact be feasible. Future research into the efficacy of RT with (and without) mismatch, offered in an online format is highly relevant, as the current pandemic and social distancing measures have already begun changing the way therapy is being offered.

Chapter VI: Conclusion

Betrayal from a romantic partner can take many forms, including sexual or emotional infidelity, abandonment or financial deception. In each of these cases, romantic betrayal can be highly stressful and has been found to result in the development of trauma-related symptoms (i.e., hypervigilance, avoidance, and intrusive thoughts), as well as anxiety and depressive symptoms in the betrayed individual (e.g., Gordon et al., 2004). Considering the shared psychological impact and symptomatology that result from the experience of betrayal and that of trauma, the diagnostic construct AD, which is a trauma- and stressor-related disorder, has been applied to better understand the repercussions of betrayal, and to determine potential treatments for this population (APA, 2013; Lonergan, Saumier, et al., 2020). The treatments typically recommended for AD include psychotherapy or anti-depressants, but little evidence for the efficacy of these treatments for AD exists, especially for AD stemming from romantic betrayal (Casey, 2014; O'Donnell et al., 2018).

RT is one psychiatric treatment that has been found to effectively reduce the symptoms of traumatic stress, addiction, specific phobia, and, more recently, AD. However, there are conflicting findings concerning RT's efficacy, with some studies finding no effect of memory reactivation with propranolol compared to placebo (e.g., Wood et al., 2015). To explain the conflicting findings, researchers have increasingly been making a case for the requirement of a mismatch between expectation and reality to trigger reconsolidation, and to subsequently impair it (i.e., Sevenster et al., 2014). While several researchers have not taken mismatch into account in their experiments, it seems that the presence or absence of mismatch may explain the controversial findings in reconsolidation studies. To date no study has systematically incorporated mismatch into RT to determine whether it improves the treatment's efficacy.

Since mismatch is a promising new avenue for improving RT, the objective of the current pilot study was to determine the feasibility of incorporating mismatch as well as the preliminary treatment effects of RT with mismatch for stressor-related symptoms and general psychological distress. To do so, participants aged 18 to 65 who experienced a betrayal by their significant other and developed an AD as a result were randomized to receive RT with mismatch or standard RT to treat their symptoms relating to the event. Standard RT involved reading a narrative of the betrayal, written in the first-person, present tense, 1-hour after administration of beta-adrenergic blocker propranolol. RT with mismatch matched the protocol for standard RT but with the incorporation of an element of novelty to the reactivation procedure during each treatment session to ensure that reconsolidation was triggered (e.g., reading the narrative in the third-person, past tense, watching a video of oneself reading the narrative).

The results indicated that incorporating mismatch is a feasible modification to RT, that is easy for participants and clinicians to adhere to and accepted by participants. The current study also demonstrates moderate preliminary treatment effects in favour of RT with mismatch. These results can inform larger scale studies of RT with and without mismatch of methodological considerations such as necessary sample size, types of mismatch events that can be implemented, potential confounds, etc. It is relevant to note that the mismatch protocol implemented in the current study has yet to be validated and no standard protocol to trigger mismatch in a clinical sample remains exists to date. Future studies should take the boundary conditions of reconsolidation into consideration, as well as the relevance of the mismatch event to the maladaptive memory, in order to ensure that reconsolidation is in fact being triggered.

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Table 1.

Design of the trial

<table>
<tr><td>Visit</td><td>T 0</td><td>T1</td><td>T2</td><td>T3</td><td>T4</td><td>T5</td><td>T6</td><td>T7</td><td>T8</td></tr>
<tr><td>Week</td><td>1</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>23</td></tr>
<tr><td>Procedure</td><td>Intake evaluation (Baseline)</td><td>Treatment session 1</td><td colspan="5">Treatment
sessions 2 to 5-6</td><td>Post-treatment</td><td>3-month Follow-up</td></tr>
<tr><td>Standard RT
(n = 7)</td><td rowspan="2">Consent process
+
Assessment of attachment injury
+
Baseline symptom measures
+
Medical evaluation</td><td rowspan="2">Symptom measures
+
Production of attachment injury script under propranolol (first treatment)
+
Randomization</td><td colspan="5">Symptom measures
+
Reading of attachment injury script under propranolol</td><td colspan="2" rowspan="2">Symptom measures</td></tr>
<tr><td>RT with mismatch
(n = 8)</td><td>Symptom measures
+
Read the trauma narrative while being filmed</td><td>Symptom measures
+
Watch the video of oneself reading the narrative</td><td>Symptom measures
+
Read the narrative and then add information to the narrative</td><td>Symptom measures
+
Read the narrative in the past tense</td><td>Symptom measures
+
Read the narrative in the past tense, 3rd person singular, while being filmed</td></tr>
</table>

Figure 1.

Participant enrollment throughout the clinical trial

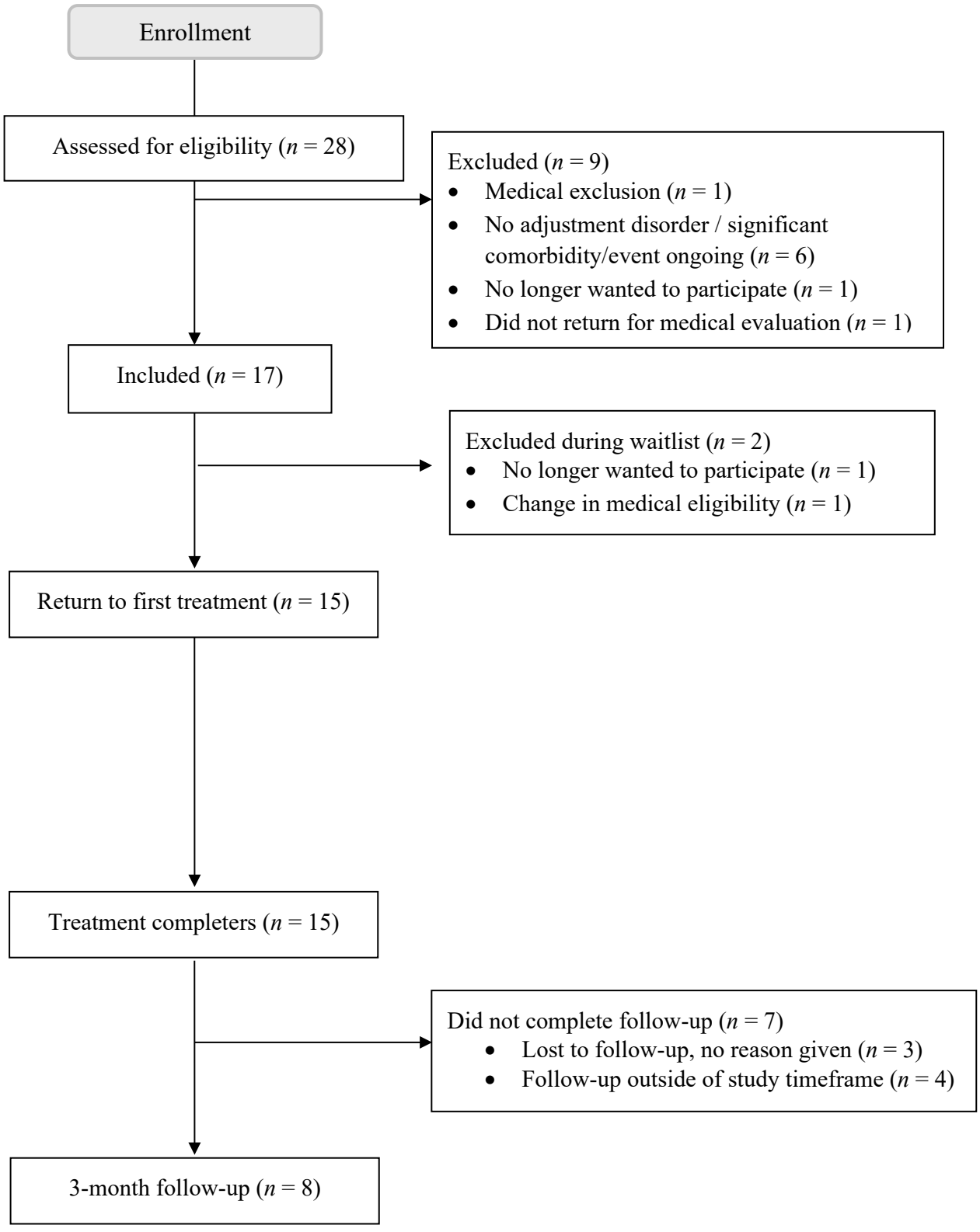


Table 2.

Sociodemographic characteristics and baseline comorbidities by group

Characteristic	Standard RT Group (n = 7)		Mismatch RT Group (n = 8)	
	M	*SD*	*M*	*SD*
Age	35.57	13.37	45.50	14.21
Education (years)	17.57	2.99	14.50	2.14
Time since betrayal event (years)	3.43	6.59	3.67	3.95
Duration of relationship total (years)	8.60	9.35	20.06	13.28
Duration of relationship pre-event (years)*	6.94	8.91	19.69	13.18
	N	*%*	*N*	*%*
Female gender	6	85.70	5	62.50
Ethnicity (% Caucasian)	3	42.90	6	75.00
Annual income (> 50k CAD$)	2	28.57	4	57.10
Relationship status (single/divorced)	4	57.20	5	62.50
Betrayal event				
Infidelity	4	57.10	5	62.50
Other (abandonment, financial deceit)	3	42.90	3	37.50
Prior / Current use of mental health services	7	100.00	7	87.50
Psychiatric diagnoses frequencies				
Major depression past	5	71.43	6	75.00
Generalized anxiety	0	0.00	1	12.50
Panic disorder	1	14.30	0	0.00
Social phobia	1	14.30	0	0.00

* Significant between-group difference (p <.05)

Table 3.

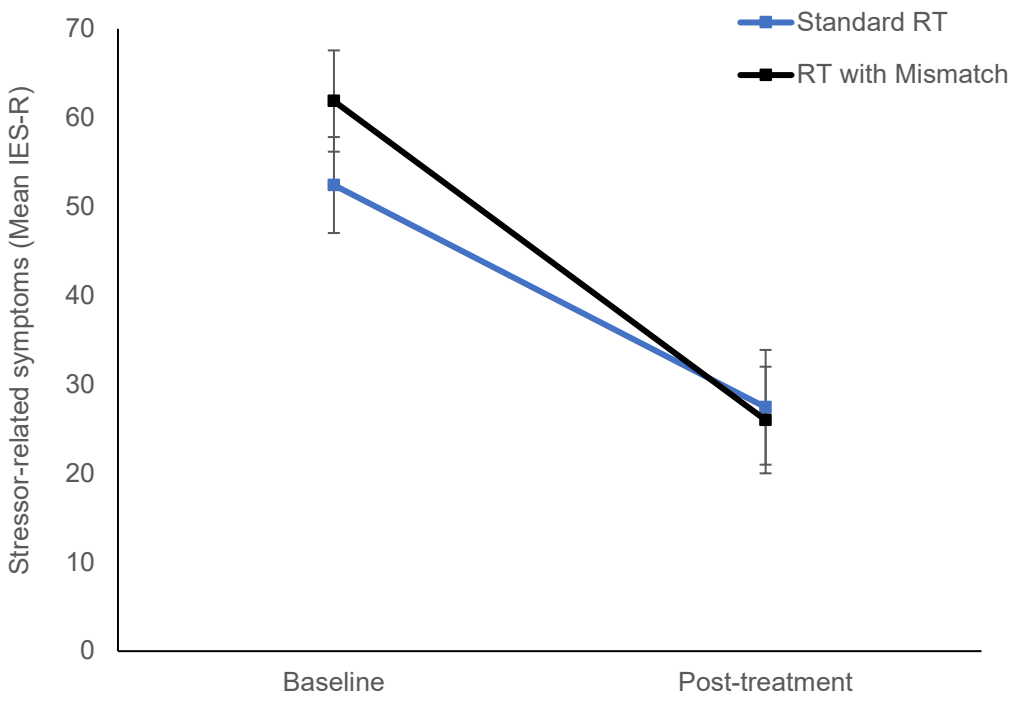
Means, standard deviations, and effect sizes for preliminary outcome measures by group

Measure	Standard Group				Mismatch Group			
IES-R total	*M*	*SD*	*N*	*d**	*M*	*SD*	*N*	*d**
Baseline	52.43	12.07	7		61.88	16.11	8	
Post-treatment	27.43	14.43	7		26.00	16.96	8	
Follow-up	26.67	8.50	3		32.60	14.31	5	
Change (Pre-post)	25.00	20.13	7		35.88	19.46	8	
Within-group effect				1.44				1.84
HSCL-25 total								
Baseline	2.40	0.42	7		2.65	0.54	8	
Post-treatment	1.69	0.58	7		1.61	0.48	8	
Follow-up	1.49	0.48	3		1.97	0.46	5	
Change (Pre-post)	0.71	0.51	7		1.03	0.70	8	
Within-group effect				1.39				1.50

*Effect size (Cohen's *d*) indicates within-group differences from pre- to post-treatment

Figure 2.

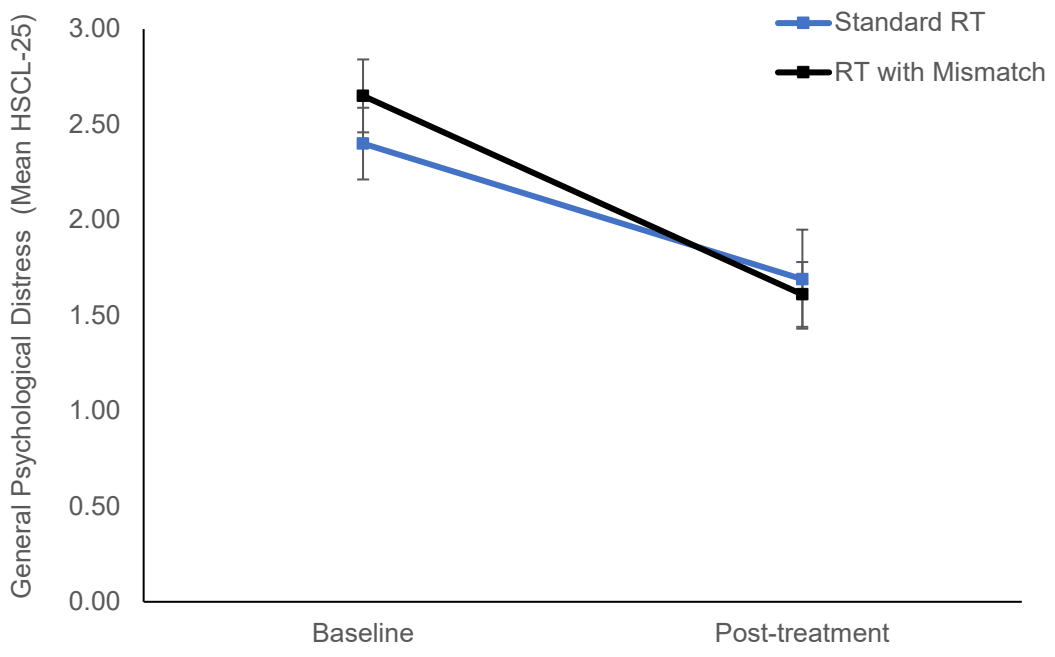
Mean(SE) event-related distress (IES-R) over time



Note. This figure demonstrates the raw mean IES-R scores at pre-treatment and post-treatment for each group.

Figure 3.

Mean(SE) general psychological distress (HSCL-25) over time



Note. This figure demonstrates the raw mean HSCL-25 scores at pre-treatment and post-treatment for each group.

Table 4.

Means, standard deviations, and within-group effect sizes for the IES-R subscales by group

Measure	Standard Group				Mismatch Group				
IES-R Intrusions	*M*	*SD*	*N*	*d**	*M*	*SD*	*N*	*d**	*d*†
Baseline	24.57	3.99	7		25.88	5.54	8		
Post-treatment	12.71	6.78	7		9.63	6.30	8		0.47
Follow-up	11.67	7.10	3		11.60	6.95	5		0.01
Change (Pre- to post)	11.86	6.15	7		16.25	6.14	8		0.71
Within-group effect				1.93				2.65	
IES-R Avoidance									
Baseline	16.00	7.00	7		20.63	7.25	8		
Post-treatment	8.71	6.73	7		11.75	8.38	8		0.40
Follow-up	11.00	3.46	3		13.80	6.42	5		0.50
Change (Pre- to post)	7.29	9.00	7		8.88	9.51	8		0.17
Within-group effect				0.81				0.93	
IES-R Hypervigilance									
Baseline	11.86	6.52	7		15.38	5.68	8		
Post-treatment	6.00	4.62	7		4.63	4.27	8		0.31
Follow-up	4.00	2.00	3		7.20	2.95	5		1.20
Change (Pre- to post)	5.86	8.61	7		10.75	6.61	8		0.64
Within-group effect				0.80				1.63	

*Effect size (Cohen's *d*) indicates within-group differences from pre- to post-treatment

† Effect size (Cohen's *d*) indicates between-group differences

Table 5.

Means, standard deviations, and within-group effect sizes for the HSCL-25 subscales by group

Measure	Standard Group				Mismatch Group				
HSCL-25 Depression	*M*	*SD*	*N*	*d**	*M*	*SD*	*N*	*d**	*d*†
Baseline	2.66	0.43	7		2.98	0.58	8		
Post-treatment	1.91	0.72	7		1.79	0.60	8		0.18
Follow-up	1.71	0.67	3		2.22	0.69	5		0.75
Change (Pre- to post)	0.75	0.70	7		1.19	0.84	8		0.57
Within-group effect				1.06				1.36	
HSCL-25 Anxiety									
Baseline	2.03	0.52	7		2.10	0.59	8		
Post-treatment	1.33	0.44	7		1.34	0.38	8		0.24
Follow-up	1.17	0.29	3		1.55	0.13	5		1.92
Change (Pre- to post)	0.70	0.42	7		0.76	0.66	8		0.11
Within-group effect				1.63				1.16	

*Effect size (Cohen's *d*) indicates within-group differences from pre- to post-treatment

† Effect size (Cohen's *d*) indicates between-group differences

Appendix A.

Inclusion and exclusion criteria for participation.

Inclusion

- **a.** Evidence of a personally signed and dated informed consent document indicating that the participant has been informed of all pertinent aspects of the study;
- **b.** Between 18 and 65 years of age at the time of consent;
- **c.** Individuals with a DSM-5 diagnosis of an adjustment disorder or chronic adjustment disorder as a result of an attachment injury, defined as an event involving the perceived betrayal, violation of trust, or abandonment by a significant other (Johnson et al., 2001).
- **d.** Individuals must be currently experiencing clinically important psychological distress as a result of the event, as defined by a score of at least 22 on the IES-R (Weiss, 2007), and a rating of at least "moderately ill" on the Clinical Global Impressions – Severity of Illness Scale (CGI-S; Guy, 1976).
- **e.** Individuals must have been in the romantic relationship for at least 6 months prior to the event;
- **f.** Must not take psychotropic medication
- **g.** Fluency in English or French;
- **h.** Live in the greater Montreal area

Exclusion:

- **a.** Systolic blood pressure <100 mm Hg;
- **b.** Cardiac rhythm below 55 beats per minute;
- **c.** A medical condition that contraindicates the administration of propranolol, e.g., Asthma, chronic obstructive pulmonary disease, cardiac insufficiency, cardiac choc, Second- or third-degree atrioventricular block, diabetes, spastic angina, auricular sinus illness, bradycardia, Raynaud's disease, severe peripheral vascular disease, untreated Pheochromocytoma, arterial hypotension, previous anaphylactic allergic shock;
- **d.** Previous adverse reaction to, or non-compliance with, beta-blocker;
- **e.** Current use of a substance that may involve potentially dangerous interactions with propranolol, including P450 2D6 inhibitors.
- **f.** Women who are pregnant or breast feeding;
- **g.** Individuals currently participating in any other form of psychotherapy (other than strictly supportive).
- **h.** Individuals who have a history of substance dependence disorder, bipolar disorder, or psychotic disorder;
- **i.** Participants judged as being at significant risk of self-injurious-/suicidal behavior;
- **j.** Participation in another drug trial within 30 days prior to the screening visit or during the study;
- **k.** Presence of any clinical condition that might interfere with the interpretation of the efficacy and safety results.

Appendix B.

Instructions for writing the memory reactivation narrative.

Attachment Injury Experience -Construction Questionnaire

Event Type: _____

We would like you to recall the memory of the event that caused you emotional hurt (i.e., to feel abandoned or betrayed) in your relationship. Please write a description of the event in the present tense, as if it were happening now, right here. Include in your description the bodily sensations you were aware of at the time. We will interview you in more detail about this experience later. You may elect to dictate your script to the interviewer if you prefer.

Sometimes it is difficult to think of something to write "on the spot". It may help to close your eyes and imagine yourself back in the situation. Try to generate the same sensations and feelings that you experienced at the time. While the image is vivid in your memory, jot down as much details of the scene and the sensations you experienced as you can remember.

Please include such details as who was there, what you were wearing, where you were, how things looked, what you heard, etc. Continue the reverse side if necessary.

_____

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Appendix C.

Impact of Event Scale-Revised (IES-R; Weiss, 2007)

Impact of Event Scale-Revised

INSTRUCTIONS: Below is a list of comments made by people after stressful life events. Answer these questions in regard to the stressful event you are seeking treatment for. Circle the number in the column to the right of each question that indicates how frequently in the past **7 days** you have had the experience described in the statement.

	Not at all	A little bit	Moderately	Quite a bit	Extremely
1. Any reminder brought back feelings about it.	0	1	2	3	4
2. I had trouble staying asleep.	0	1	2	3	4
3. Other things kept making me think about it.	0	1	2	3	4
4. I felt irritable and angry.	0	1	2	3	4
5. I avoided letting myself get upset when I thought about it or was reminded of it.	0	1	2	3	4
6. I thought about it when I didn't mean to.	0	1	2	3	4
7. I felt as if it hadn't happened or wasn't real.	0	1	2	3	4
8. I stayed away from reminders of it.	0	1	2	3	4
9. Pictures about it popped into my head.	0	1	2	3	4
10. I was jumpy and easily started.	0	1	2	3	4
11. I tried not to think about it.	0	1	2	3	4
12. I was aware that I still had a lot of feelings about it, but I didn't deal with them.	0	1	2	3	4
13. My feelings about it were kind of numb.	0	1	2	3	4

14. I found myself acting or feeling like I was back in that time.	0	1	2	3	4
15. I had trouble falling asleep.	0	1	2	3	4
16. I had waves of strong feeling about it.	0	1	2	3	4
17. I tried to remove it from my memory.	0	1	2	3	4
18. I had trouble concentrating.	0	1	2	3	4
19. Reminders of it caused me to have physical reactions, such as sweating, trouble breathing, nausea or a pounding heart.	0	1	2	3	4
20. I had dreams about it.	0	1	2	3	4
21. I felt watchful and on guard.	0	1	2	3	4
22. I tried not to talk about it.	0	1	2	3	4

Appendix D.

Hopkins Symptom Checklist (HSCL-25; Winokur et al., 1984)

Hopkins Symptom Checklist (HSCL-25)

INSTRUCTIONS: Below is a List of problems and complaints that people sometimes have. Please read each one carefully. After you have done so, please put a check (✓) in one of the four boxes to the right that best describes **how much that problem has bothered you during the last week (7 days), including today .**
Check only one box for each problem and do not skip any items. Make your checks carefully. If you change your mind, erase your first mark completely. Read the example below before beginning.

EXAMPLE:

	1 Not At All	**2** A Little Bit	**3** Quite A Bit	**4** Extremely
1. Backaches		✓		

HOW MUCH ARE YOU BOTHERED BY:	**1** Not At All	**2** A Little Bit	**3** Quite A Bit	**4** Extremely
1. Headaches				
2. Nervousness or shakiness inside				
3. Faintness or dizziness				
4. Loss of sexual interest or pleasure				
5. Spells of terror or panic				
6. Feeling low in energy or slowed down				
7. Thoughts of ending your life				
8. Feeling restless				
9. Trembling				
10. Poor appetite				
11. Crying easily				
12. A feeling of being trapped or caught				
13. Suddenly scared for no reason				
14. Blaming yourself for things				
15. Feeling lonely				
16. Feeling blue				
17. Worrying too much about things				
18. Feeling no interest in things				
19. Feeling fearful				
20. Heart pounding or racing				
21. Trouble falling asleep or staying sleep				
22. Feelings of worthlessness				
23. Feeling hopeless about the future				
24. Feeling everything is an effort				
25. Feeling tense or keyed up				