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A Two-Factor Model of Relapse/Recurrence Vulnerability in Unipolar Depression

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Abstract

The substantial health burden associated with Major Depressive Disorder is a product of both its high prevalence and the significant risk of relapse, recurrence and chronicity. Establishing recurrence vulnerability factors (VFs) could improve the long-term management of MDD by identifying the need for further intervention in seemingly recovered patients. We present a model of sensitization in depression vulnerability, with an emphasis on the integration of behavioral and neural systems accounts. Evidence suggests that VFs fall into two categories: dysphoric attention and dysphoric elaboration. Dysphoric attention is driven by fixation on negative life events, and is characterized behaviorally by reduced executive control, and neurally by elevated activity in the brain's salience network. Dysphoric elaboration is driven by rumination that promotes over-general self and contextual appraisals, and is characterized behaviorally by dysfunctional attitudes, and neurally by elevated connectivity within normally-distinct prefrontal brain networks. While, at present, few prospective VF studies exist from which to catalogue a definitive neurobehavioral account, extant data support the value of the proposed two-factor model. Measuring the continued presence of these two VFs during recovery may more accurately identify remitted patients who would benefit from targeted prophylactic intervention.

Keywords

Depression; Relapse; Recurrence Vulnerability; Sensitization; Reactivity

With empirical evidence supporting pharmacologic (Rush et al., 2006) and psychotherapeutic (Hollon et al., 2005) treatment of the acute phase of Major Depressive Disorder (MDD), patients and clinicians increasingly face the challenge of averting future episodes. Consistent with the tenets of prevention science (Munoz, Cuijpers, Smit, Barrera,

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& Leykin, 2010), a potentially productive strategy is to identify the stress sensitivity factors that predispose individuals to relapse and recurrence. In particular, the identification of malleable vulnerability factors (VFs) may allow for personalized risk assessment following symptom remission and the provision of prophylactic, individualized interventions. While VFs remain understudied in the research literature, emerging cognitive-behavioral and neuroimaging studies have begun to provide parallel accounts of MDD vulnerability, revealing potential avenues for effective risk assessment and intervention. In this article, we outline the rationale for the integration of these two literatures into a two-factor model of depression vulnerability.

Depression vulnerability has been defined in terms of increased risk for re-emergence of symptoms (relapse) or a new episode (recurrence) following a period of recovery (APA, 2000; Frank et al., 1991). As recently articulated (Monroe & Harkness, 2011), the dominant focus on relapse/recurrence ignores the large percentage of patients who experience only a single lifetime episode. This disjunction suggests a sensitization process that distinguishes single episode vulnerability from risk for a more chronic course of illness. In characterizing this sensitization, the mutually-reinforcing relationship between negative life events and depression vulnerability across the lifespan has been a fruitful area of investigation (Liu & Alloy, 2010). Such vulnerability is ultimately gauged by the return of depressive episodes, either in terms of relapse following the incomplete remission of depressive symptoms, or in the form of recurrence following successful remission. However, the literature distinguishing relapse and recurrence risk is sparse, and vulnerability for relapse and recurrence are likely at least partially determined by a common set of VFs. For this reason, we posit our model as potentially indicative of both relapse and recurrence vulnerability, at least until further research provides greater evidence for distinct risk profiles underlying the two forms of vulnerability.

To date, most established VFs, such as personality (Klein, Kotov, & Bufferd, 2011), genetics (Talati, Weissman, & Hamilton, 2013), and clinical history (Judd et al., 1998), reflect largely fixed patient factors. To add to these conceptualizations, we propose two VFs representing different aspects of cognitive dysregulation: *dysphoric attention* and *dysphoric elaboration*. Positioned between environmental stress and the expression of depressive symptoms, it is our hope that these constructs will help to characterize sensitization effects as the dynamic product of sequenced dysregulations. If measurement of these dysregulations can be refined, it could help to reveal enduring vulnerability following MDD remission/recovery.

The Two-Factor Sensitization Model

The two-factor model is intended to be integrative, describing dynamic mechanisms of initial stress sensitivity and subsequent sensitization in MDD. Stress is proposed to be the product of detecting threats and appraising them as unmanageable, in keeping with appraisal theories of emotion (Lazarus & Folkman, 1984). For example, one might experience adverse life events such as losing one's job or suffering a personal injury. While such events are relatively universal examples of adversity, the stress generated by these events varies between people on a continuum ranging from resilience to vulnerability. The central claim

of the model is that one's stress in the face of adverse life events depends on how specific features of these events are integrated into a person's interpretive context, a process biased both by what kinds of features capture attention, and how one subsequently elaborates on attended features. In the example of losing one's job, one may fixate on the mortifying feelings of being fired or on the visceral sense of relief to be leaving an acerbic work environment. Subsequently, one might appraise oneself dysphorically as being a failure, or euphorically as being a bit wiser for having gone through the experience. Such appraisals then reinforce attentional habits to fixate on mood-congruent features of events, forming an interpretive cycle between attention and elaboration. The central prediction of the two-factor model is that sensitization occurs because of increased coupling between dysphoric attention and elaboration. This coupling serves to elevate relapse/recurrence risk with each subsequent episode, as even relatively minor signs of adversity gain the power to activate powerful dysphoric elaborations.

The proposal of dysphoric attention and elaboration as VFs acknowledges that vulnerability stems from both extrinsic and intrinsic sources. There is substantial evidence that while major stressors promote the onset of initial depressive episodes, minor stressors become increasingly predictive of relapse/recurrence with successive episodes, indicating a potential sensitization process (Monroe & Harkness, 2005). With each episode, depression vulnerability and the arising of life stressors become increasingly correlated, suggesting a lowered threshold for stress appraisals as a consequence of depressive life history (Liu & Alloy, 2010). In effect, each episode engenders stress sensitization, leaving apparently recovered individuals at elevated risk for future depressive episodes, although the mechanisms by which such sensitization occurs are largely unknown.

The two-factor model proposes a process for how such stress sensitization occurs (Figure 1). Sensitization occurs as a consequence of *fixation* and *rumination*: fixation favors sustained representation of negative over positive features of events, leading to weak associations between simultaneously represented negative features. Rumination then integrates concrete negative feature representations into abstract dysphoric schema about one's self, future, and role in the world, e.g., "I'm a failure". The presence of dysphoric schemas shift a person's attention towards mood congruent content and increases the associative potential of features from novel negative events, enhancing dysphoric fixation and reinforcing dysphoric attitudes.

Traditionally, cognitive models of sensitization implicate rumination as a monolithic cognitive process in which vulnerable individuals focus attention on experienced stressors and their implications (Nolen-Hoeksema, Wisco, & Lyubomirsky, 2008). Our model suggests that this definition of rumination might conflate 2 VFs, attention and elaboration, which have distinct roles in the sensitization process. Dysphoric attention to stressors constitutes an early VF, increasing the relative salience of negative life events (Armstrong & Olatunji, 2012; Peckham, McHugh, & Otto, 2010; Sanchez, Vazquez, Marker, LeMoult, & Joormann, 2013). This salience promotes a temporally-extended attentional capture by negative events that we will refer to as *fixation*. We propose that dysphoric attention is common to both first episode and recurrent forms of depression. However, fixation on negative life events also promotes dysphoric elaboration, skewing the integration of events

to form dysphoric schema about the self, the future and the world. Such schema provide a conceptual anchor that unify and normalize the interpretation of further adverse experiences.

Sensitization is hypothesized to occur when dysphoric elaboration binds fixated negative events with negative, self-referential implications – it is this more elaborative rather than attentional process that we will refer to as rumination. Rumination creates strong associations between negative events and a centralized self-concept (Lyubomirsky & Nolen-Hoeksema, 1995), leading to generalized dysphoric attitudes towards the self, one's future, and one's place in the world, in keeping with cognitive models of depression (Beck, 1970). These attitudes are relatively independent of changing environmental contexts as they refer to stable, global, and internal properties (Seligman, Abramson, Semmel, & Von Baeyer, 1979) As such, dysphoric attitudes are themselves depressogenic, serving as semantic attractors for novel negative life events, magnifying the perceived implication of minor life events as confirming pre-existing dysphoric attitudes. These stress-emergent negative schemas manifest in the form of cognitive reactivity, a pattern of dysphoric elaboration that acts as a second VF (Teasdale, 1999).

As an example, let us consider James, an accountant in his mid 30's whose mother passes away after an unexpected illness. While his siblings grieve and adapt to the loss, James *fixates* upon his mother's passing, how she won't be there to see his kids grow up or celebrate his promotion within the firm. He notices that his energy at work starts to flag and he finds himself making mistakes on his clients' files. To James, each day seems to pass with little to look forward to or enjoy. Throughout this time, James *ruminates* on why he alone seems to have these negative thoughts and feelings, and wonders whether he lacks the ability to thrive in the world without his mother's support and guidance. As time passes, James starts to return to his old self, but now sees the world differently. Seemingly minor upsets such as spilling his coffee one morning immediately bring to mind thoughts of inadequacy and worthlessness, serving as one more confirmatory example of his low view of self. Left unchecked, such seemingly innocuous triggers put James at a heightened risk for the re-emergence of depression compared to before his bereavement. Critically, it is the combination of fixation on negative life events combined with ruminative self-elaboration that characterize the sensitization process rather than these factors operating in isolation.

The idea that multiple cognitive factors are involved in depression is not novel, having been described in recent reviews (Gotlib & Joormann, 2010; Jacobs, Reinecke, Gollan, & Kane, 2008). However, while such reviews cast depression vulnerability in terms of a failure for explicit reflective processes to inhibit pre-existing dysphoric associations (Beevers, 2005), the two-factor model seeks to describe how such failures allow enduring conceptual associations to form insidiously, progressing from maladaptive fixation on negative experiences to entrenched global attitudes. While this is a complex and cyclical process, the model can be broken down into four major assumptions that lead to a prediction of stress sensitization in depression:

1. *Vulnerability operates at both concrete and implicational levels of processing.* The central assumption of the model is drawn from construal theory, which proposes that human cognition operates at both concrete and implicational levels of construal

to determine subjective experience (Barnard & Teasdale, 1991; Trope & Liberman, 2010). Experience is therefore subject to two distinct sources of bias, attention biases towards negative events, and schematic biases about how such events inform our understanding of ourselves in the world. The ‘starting values’ for such biases are not arbitrary, but are likely influenced by a host of genetic, developmental, and environmental factors.

2. *Dysphoric processing biases are malleable.* It is likely that people develop resilience or sensitivity to stress over time, to their benefit in the presence of social and clinical support, or to their detriment following loss, isolation or trauma. Sensitization in this model is defined as the dysphoric tuning of affective integration biases.
3. *Attention and schematic biases have independent tuning mechanisms.* Attention bias towards life events is tuned through *fixation* on negative events, repeated failure to disengage from negative information despite normal thresholds for the detection of such events (Gotlib & Joormann, 2010). Schematic bias is tuned through *rumination*, a recursive analysis of one’s self, future and environment. To the extent that an analytic focus weakens positive attitudes and reinforces negative attitudes, it promotes dysphoric elaboration, engendering global dysphoric attitudes (Rimes & Watkins, 2005).
4. *While fixation and rumination and analytic focus are distinct cognitive operations, they are inter-related through their effects.* Fixation on negative events provides rich opportunities for dysphoric elaboration (Koster, De Lissnyder, Derakshan, & De Raedt, 2011). Repeated conceptual analysis of the causes and consequences of negative events then consolidates negative associations in memory as dysphoric schemas. Conversely, once such schemas supersede the optimistic elaborative biases observed in healthy individuals, dysphoric elaboration supports attentional capture by schema-congruent depressive events, reducing the plasticity of the representational system (Pittenger & Duman, 2007).

Integrating many of the points above, the major prediction of the model is that dysphoric elaboration is a consequence of sustained dysphoric attention, representing a sensitization mechanism for risk of relapse/recurrence. Most individuals begin life with resilience against depression, in the form of positively-skewed, self-serving interpretive biases that are largely absent in depressed samples (Mezulis, Abramson, Hyde, & Hankin, 2004). Even before exposure to major stressors, the tuning of attention and interpretive biases likely varies between individuals as a function of genetic, developmental, social, and strategic factors. Early vulnerability to depression likely plays out through fixation on negative life events, creating dissonance between such negative events and positive implicational biases about the self, world, and future. While it may be possible that fixation alone could lead to an initial depressive episode, it seems more likely that initial vulnerability involves the intersection of fixation tendencies with major life stressors. In cases where major life stressors are present, pervasive exposure to negative events dominates subjective experience, leading to the onset of the first depressive episode. During this time, factors such as personality (Shea & Yen, 2005), regulatory strategy (Silk, Steinberg, & Morris, 2003),

explanatory style (Nolen-Hoeksema, Girgus, & Seligman, 1986), all of which are affected by both genetics and environment throughout development, serve to determine the tendency to fixate and ruminate on these major life stressors.

To the extent that one's regulatory habits promote fixation and rumination, sensitization begins through the gradual deterioration of positive implications as they are updated to reflect negative life experience. Rumination populates subjective experience with negative implications, lowering the threshold needed for negative life events to create a net dysphoric experience conducive to MDD recurrence. With each depressive episode, fixation on negative events provides additional opportunities for rumination, disrupting positive attitudes and entrenching global negative attitudes about the self, future, and world. Conversely, increased dysphoric elaboration feeds back onto attention processes, imbuing negative tone to ambiguous situations and lowering the threshold for stress perception. In this way, progressively tighter coupling between dysphoric attention and elaboration serves to explain risk elevation with subsequent depressive relapses/recurrences, a theory that is supported by contemporary clinical and neuroimaging investigations of depression vulnerability.

Clinical Research Supporting the Two-Factor Model

The two factor model makes a series of empirical claims about the relationship between attention, elaboration, and relapse/recurrence vulnerability. For each VF, numerous operationalizations are possible. For each of dysphoric attention and dysphoric elaboration, some of the central operational paradigms and their intended vulnerability markers are summarized in Table 1. Through research using these paradigms, each of the model's claims has found some measure of support in the empirical literature; these claims, examples of the research supporting them, and future research directions are summarized in Table 2. Below, we review these findings and address the need for further research in greater depth.

Claim #1: Vulnerability operates at concrete and implicational levels of processing

We posit that dysphoric attention is a VF that reflects sensitivity to negative life events, while dysphoric elaboration is a VF that reflects more general dysphoric attitudes. The separation of attentional and elaborative VFs has historical precedent in the depression research literature. For example, the tendency to rehearse dysphoric attitudes about the self has been linked to depressive symptoms, an association independent from the effects of negative life events (Smith, Ingram, & Roth, 1985). This finding led researchers to distinguish between concrete thoughts tied to features of negative events themselves, and more abstract thoughts about the implications of these features in supporting narratives of global, chronic difficulties (Avison & Turner, 1988). In this way, the seeds of the attention/elaboration distinction were formed.

Subsequently, dysphoric attention has been theorized to underlie sensitivity to negative life events, predicated upon an associative bias for the processing of negative information and a deficit of reflective attentional control (Beevers, 2005; Carver, Johnson, & Joormann, 2008). Consequently, depression vulnerability has been linked to exaggerated, temporally-extended attentional capture by negatively-valenced stimuli and subsequent behavioral inhibition

(Caseras, Garner, Bradley, & Mogg, 2007; Fritzsche et al., 2010; Leyman, De Raedt, Schacht, & Koster, 2007). Paradigms for tracking dysphoric attention include the dot-probe task, emotional stroop, spatial cueing, and eye tracking tasks (Table 1). Unlike most attentional capture paradigms, in which attention is directed quickly to a salient target, in depression such capture occurs slowly; relative to healthy controls and patients with anxiety, depressed participants linger longer on negative stimuli (Mogg, Bradley, & Williams, 1995), maintaining negative representations that are susceptible to further cognitive elaboration. Dysphoric attention therefore appears to be a deficit in the voluntary control of attention rather than some form of subliminal attentional capture; indeed, depressed participants show little distinction from controls when stimuli are presented at onsets less than 1 sec in duration (Bradley, Mogg, & Lee, 1997).

While deficits in attention control are apparent in response to negative external stimuli, vulnerability also extends to preoccupation with negative ideation (Koster et al., 2011). Dysphoric elaboration is most commonly measured through mood-evoked *cognitive reactivity*. In such paradigms, negative mood inductions increase the endorsement of global, dysfunctional attitudes in people with a history of depression, but not in people who have never been depressed (Ingram, Atchley, & Segal, 2011; Jeanne, Gross, Persons, & Hahn, 1998; Teasdale & Cox, 2001). Importantly for dysphoric elaboration's status as a VF, cognitive reactivity predicts failure to recover from depression (Williams, Healy, Teasdale, White, & Paykel, 1990), and is predictive of depressive relapse (Segal et al., 2006). In addition to cognitive reactivity paradigms, dysphoric elaboration is also measured through scrambled sentence completion tasks, self-reported dysfunctional attitudes, and avoidance of negative affect (Table 1).

Claim #2: Dysphoric processing biases are malleable

Substantial recent research has focused on the modification of the two VFs, creating two robust but often separate research literatures. Since attention bias can be manipulated rapidly, it is perhaps easier to demonstrate its malleability. Indeed, negative attention bias appears to be reliably induced by repeated trials of focusing a person's attention on negative stimuli following simultaneous presentation of negative and neutral stimuli (MacLeod, Rutherford, Campbell, Ebsworthy, & Holker, 2002). Conversely, it also appears possible to use these attention-training paradigms to reduce negative attention bias both in moderately-depressed college students (Wells & Beevers, 2010), and in select cases of acutely depressed individuals (Papageorgiou & Wells, 2000; Wells et al., 2009).

Dysphoric elaboration consists of entrenched negative attitudes, whose malleability is perhaps more difficult to establish empirically. However, cognitive bias modification interventions have been growing in popularity, and a recent meta-analysis of such interventions found moderate effects on elaborative biases in addition to attentional biases (Hallion & Ruscio, 2011). We may also infer malleability of dysphoric elaboration through clinical studies in which depressive thinking styles change following interventions designed to reduce rates of relapse/recurrence (Hollon 2005; Teasdale 2000).

For example, Mindfulness Based Cognitive Therapy (MBCT) is designed to reduce relapse/recurrence vulnerability by limiting dysphoric elaboration (Teasdale et al., 2000). Indeed,

mindfulness training has been linked to reduced rumination scores in community participants undergoing mindfulness-based stress reduction (MBSR; Deyo, Wilson, Ong, & Koopman, 2009), and in patients with recurrent depression (Ramel, Goldin, Carmona, & McQuaid, 2004). In an active control study, MBCT reduced rumination significantly more than a relaxation control in a depressed college sample (Jain, Shapiro, Swanick, Roesch, Mills, et al., 2007). In another study, depressed patients were asked to recall a list of mixed-valence words before and after a social stress induction. While control participants reported longer trains of negative words during recall following the stressor, MBCT group members showed the opposite pattern, actually reducing their tendency to recall successive negative words (Van Vugt, Hitchcock, Shahar, & Britton, 2012). Taken together, this evidence is suggestive of the potential for therapeutic interventions to reduce dysphoric elaboration, a testament to the malleability of this second VF.

Claim #3: Attention and schematic biases have independent tuning mechanisms

Specifically, we suggest that dysphoric attention is tuned through fixation, while dysphoric elaboration is tuned through rumination. Furthermore, we argue that fixation and rumination are distinct, albeit interrelated, constructs. One challenge in using current research to distinguish between fixation and rumination is that many efficacious interventions attempt to address both of these biases concurrently, making it difficult to track construct-specific changes. For example, both mindfulness-based interventions (Kabat-Zinn, 1990; Segal, Williams, & Teasdale, 2002) and metacognitive therapy (Papageorgiou & Wells, 2000) employ a combination of attention training practices and training on the importance of limiting dysphoric rumination. Nevertheless, paradigms that focus more purely on fixation and rumination do exist. Training in fixation on negative stimuli leads to greater depressive symptoms following a stressor than training in fixation on neutral stimuli (MacLeod et al., 2002). Conversely, training in fixation on positive stimuli leads to reduced attention towards dysphoric stimuli (Wadlinger & Isaacowitz, 2008), and training-reduced negative attention bias mediates reductions in depressive symptoms in moderately-depressed college students (Wells & Beevers, 2010), and in case studies of acutely depressed individuals (Wells et al., 2009). Indeed, such data are behind recent claims that affect-biased attention constitutes a form of emotion regulation or dysregulation in its own right (Todd, Cunningham, Anderson, & Thompson, 2012; Wadlinger & Isaacowitz, 2011).

Comparably, studies of rumination's impact on emotional health have found that rumination promotes overgeneral memory in depression (Watkins & Teasdale, 2001), compromises working memory capacity in both depressed adults (Watkins & Brown, 2002) and dysphoric young adults (Philippot & Brutoux, 2008), reduces sleep quality (Guastella & Moulds, 2007), and impairs interpersonal problem solving (Yoon & Joormann, 2012). In a recent examination of rumination and mindfulness inductions, rumination led to greater negative affect and physiological arousal whereas mindfulness increased positive affect and parasympathetic activity (Gilbert & Gruber, 2014), suggesting that elaborative tuning can occur bi-directionally to promote either wellness or psychopathology. Additionally, a study of MBCT with formerly depressed participants found that rumination scores were reduced following MBCT, with residual levels of rumination post-treatment predicting depressive relapse over a 1 year follow up (Michalak, Holz, & Teismann, 2011). To the extent that

rumination can be reduced, such tuning may be protective in the struggle against reemergence of depressive symptoms following episode.

Given evidence of both fixation and rumination tuning, we may question how independent these mechanisms truly are. Although fixation and rumination may seem similar in their preoccupation with negative experience, experimental evidence supports a distinction between these cognitive processes. In empirical investigations, rumination is related to, but not identical to fixation (Donaldson, Lam, & Mathews, 2007; Joormann, 2006; Joormann, Dkane, & Gotlib, 2006; Joormann & Gotlib, 2008), with rumination scores accounting for 10–20% of the variance in attention bias scores after controlling for depressive symptom severity.

One reason for this modest overlap is that fixation appears to be an abnormality of selection rather than elaboration. In other words, fixation involves the inhibition of attentional capture by positive information as well as exaggerated capture by negative information. Unlike the operationalization of attention capture in the broader cognitive literature, fixation appears to occur over more protracted time courses of at least a second following stimulus onset, unlike the early selection biases towards threat stimuli that is found in anxiety disorders (Bradley et al., 1997). However, this 1 second time course is still far different from a chronic pattern of conceptual evaluation. For example, a meta-analysis of eye-tracking studies in affective disorders observed that relative to anxiety disorders, depression is uniquely characterized by both reduced orienting towards positive stimuli and maintenance of gaze towards these stimuli, in addition to exaggerated maintenance towards negative stimuli (Armstrong & Olatunji, 2012). By contrast, brooding, the dysphoric aspect of rumination, is characterized primarily by items expressing some dissatisfaction with the self, rather than a pre-occupation with the inciting negative events themselves (Armey et al., 2009; Joormann et al., 2006). Consistent with this account, induction of a ruminative focus in patients with depression increased self-ratings of worthlessness and incompetence (Rimes & Watkins, 2005). Thus from a content analysis, the constructs of fixation and rumination appear to have separate targets.

Granting that there is some independence between fixation and rumination, research has begun to assess how rumination and fixation separately mediate vulnerability. For example, the magnitude of dysphoric fixation in patients with MDD has recently been associated with slower recovery from sadness in subsequent mood induction (Clasen, Wells, Ellis, & Beevers, 2013; Sanchez et al., 2013). In a study of adolescents with a history of MDD, rumination was predicted by past depressive episodes, but also predicted episode return and duration (Abela & Hankin, 2011). Studies of this kind provide naturalistic evidence that fixation and rumination can be tuned over time to modify levels of risk.

The presence of distinct contributing mechanisms may help to explain why both MDD remission (Guidi, Fava, Fava, & Papakostas, 2011) and prevention of relapse/recurrence (Segal et al., 2010) are better achieved through combinations of therapeutic interventions compared to monotherapy, as different treatments may target different vulnerability factors. By this logic, identification of dominant VFs may be important for selecting the highest priority clinical intervention. For example, patients whose VFs primarily suggest dysphoric

attention may benefit most from attention bias modification (Browning, Holmes, Charles, Cowen, & Harmer, 2012) or maintenance antidepressant medication (ADM), whereas those demonstrating mixed VFs may benefit additionally from cognitive therapy (CT) or mindfulness-based cognitive therapy, treatments that focus on building metacognitive awareness (Teasdale et al., 2002). Further research will be needed to validate algorithms for matching clinical interventions to particular VF patterns.

Claim #4: Fixation and rumination have mutually reinforcing effects

Fixation and rumination may be mutually reinforcing in provoking depression vulnerability, with a potential causal pathway moving from fixation to rumination to increased vulnerability. This causal hypothesis is based on findings from a pilot study (n=4) of therapeutic attention training in recurrent depression that led to reduced rumination scores over a 12 month follow up (Papageorgiou & Wells, 2000), while Donaldson et al. (2007) found no immediate effect of a rumination induction on levels of dysphoric fixation. Nevertheless, when rumination and fixation are measured concurrently, they do appear to be moderately related, with 10–20% shared variance in depressed samples, and a more moderate 6–10% shared variance in subclinical samples (Everaert et al., 2014; Everaert, Tierens, Uzieblo, & Koster, 2013). However, even within such samples, rumination mediates the relationship between fixation and subsequent memory biases, supporting the notion of a causal pathway from fixation to rumination. Longitudinal research is needed to investigate the possibility of a tightening correspondence between attention and elaboration with increasing episode vulnerability. In particular such studies could evaluate whether there is a temporal precedence to changes in dysphoric attention and elaboration that would imply a causal flow.

The connection between fixation and rumination does help to explain the idiosyncrasies of attentional biases in depression. While remitted depressed patients demonstrate a compromised ability to disengage attention from sad faces in dot-probe tasks (Joormann & Gotlib, 2007), these biases are only apparent following long (> 1000 msec) exposure periods to dysphoric words (Fritzsche et al., 2010). This prolonged attentional requirement and neural response suggests a slower, elaborative mechanism of vulnerability that is distinct from stimulus-driven, dysphoric attentional capture that is observed in anxiety disorders. Instead, the ‘lingering gaze’ in remission may reflect an attentional bias reinforced by cognitive elaboration.

Furthermore, dysphoric elaboration appears to influence attention to external events. For example, remitted depressed patients tend to rate neutral faces as possessing negative affective tone more often than controls (Bhagwagar, Cowen, Goodwin, & Harmer, 2004; Leppanen, Milders, Bell, Terriere, & Hietanen, 2004). In this way, dysphoric elaboration may shape behavior to increase the likelihood of stressful life experiences (Liu & Alloy, 2010), and also impose powerful retrospective biases that act as a ‘late selector’ of negative attributes from complex social events (Hammen, 2005).

Prediction: Sensitization occurs because dysphoric attention becomes conflated with elaboration

While there is strong evidence to support a connection between dysphoric attention and elaboration, there is relatively little evidence to support a causal flow between the two. However, given the evidence presented thus far, a reasonable prediction would be that chronic dysphoric attention facilitates dysphoric elaboration, which leads to tighter coupling between the two VFs. This coupling constitutes a sensitization to negative experience that increases the risk of depressive relapse/recurrence. Consistent with this view, a year-long study of 6–14 year olds found that those possessing low self-esteem and high dysfunctional attitudes demonstrated the greatest elevation in depressive symptoms following elevations in daily hassles compared to others in the same cohort (Abela & Skitch, 2007). It is this insidious coupling between dysphoric attention and elaboration of even minor events that elevates relapse/recurrence vulnerability. Within this framework, dysphoric elaboration may constitute a process supporting an existing theory that cognitive vulnerabilities contribute to the appraisal of ambiguous or seemingly minor stressors as highly stressful events, which in turn compromise a person's sense of well-being (Liu & Alloy, 2010). This iterative dynamic interplay between daily stressors, fixation on these stressors, and their amplification via cognitive reactivity may well be responsible for increased vulnerability to episode return with successive depressive episodes.

A number of basic science paradigms have been used to examine the potential sensitization relationship between dysphoric attention and elaboration. A central sensitization mechanism is the withdrawal of engagement with positive life events in the face of stress. For example, emotional stressors appear to reduce reward responsiveness (Bogdan & Pizzagalli, 2006; Foti & Hajcak, 2010). Thus, exposure to salient stressors through dysphoric attention may initially reduce processing of positive stimuli, a sign of early relapse/recurrence vulnerability. Blunting of the neural response to reward predicts subsequent depression vulnerability in female adolescents (Bress, Foti, Kotov, Klein, & Hajcak, 2013), an effect particularly evident in recurrent compared to early episode depression (Hall, Milne, & Macqueen, 2013). Such blunting may represent the entrenchment of attentional biases to exclude positive features of life events.

As stress-related disengagement from positive features of events intensifies, dissonance is created between a person's positive self-construal and the lack of such positivity in daily life. A proclivity for rumination may then serve to erode these positive attitudes, such as the personalization of negative experiences, rather than seeing them as the consequence of external circumstances (Ciesla, Felton, & Roberts, 2011; Smith & Alloy, 2009). Accordingly, the self-schema model of depression (Dance & Kuiper, 1987), is predicated on research demonstrating that conventional, positive self-schema roles are disrupted both in MDD, but also in people vulnerable to MDD (MacDonald, Kuiper, & Olinger, 1985). In the Macdonald et al. study, participants with both mild and moderate depressive symptoms showed less consistency than control participants in their self-ratings of neutral and dysphoric trait adjectives, suggesting a destabilization of self-referential attitudes. Similarly, greater anhedonic symptoms in depression have been associated with reductions in positive, self-enhancing bias (Dunn, Stefanovitch, Buchan, Lawrence, & Dalgleish, 2009).

We propose that sensitization occurs as rumination erodes positive attitudes and strengthens dysfunctional attitudes. In keeping with this idea, multiple clinical studies suggest that dysphoric elaboration is the dominant predictor of relapse/recurrence in patients with multiple previous MDD episodes (Halvorsen, Wang, Eisemann, & Waterloo, 2010), even when compared to patients with a single prior episode (Yamamoto, Yamano, Shimada, Ichikawa, & Nakaya, 2014). As self-schemas are repeatedly disrupted, dysphoric elaboration may become habitual, reducing awareness of such associations and thereby reducing opportunities to engage in self-regulation. For example, healthy controls exposed to mood challenge demonstrate increased negative implicit attitudes, but remitted participants maintain a pre-existing negative bias that was found prior to induction (Meites, Deveney, Steele, Holmes, & Pizzagalli, 2008). This finding suggests an ‘always-on’ negative self association that persists following remission.

The consequence of powerful dysphoric elaboration is that nominally benign stressors become triggers for the rehearsal of dysphoric attitudes (Segal, Williams, Teasdale, & Gemar, 1996). Supporting this idea, the number of non-severe adverse life events appears to predict new episodes of recurrent depression (Monroe et al., 2006), suggesting that the severity of adversity is less important than one’s interpretations of any adversity. Instead, it is possible that the importance of negative features of even minor stressors is exaggerated through dysphoric elaboration. Indeed, catastrophising is a unique predictor of depressive symptoms in chronic pain patients, even when controlling for other forms of responding such as distraction, dissociation, or re-appraisal (Sullivan & D’Eon, 1990). Conversely, MBCT, an intervention which appears to function through the reduction in dysphoric elaboration (as elaborated in claim 2 above), has its greatest prophylactic efficacy in patients with 3 or more past episodes of depression (Ma & Teasdale, 2004), consistent with elaboration driving vulnerability in later but not earlier episodes of recurrent depression.

The claims and predictions discussed above suggest a number of fruitful research questions. The overarching need in evaluating the two-factor model will be the simultaneous measurement of both dysphoric attention and elaboration within a single experimental paradigm, which, if conducted over multiple time points would allow for the explicit modeling of the relationship between adverse life events, dysphoric attention and elaboration, and their relationship to future symptom or episode status.

A Neural Systems Account of the Two-Factor Model

The findings reviewed above provide intriguing evidence that dysphoric elaboration may arise as a progression from dysphoric attention, elevating relapse/recurrence risk as the two VF processes become more densely interdependent with each episode. While more behavioral research is needed to substantiate this claim, neuroimaging research on depression vulnerability also speaks to the idea of conflated cognitive processes in depression vulnerability.

Neural Mechanisms of Dysphoric Attention

Maladaptive cognitive processes observed in acute MDD may persist in the form of dysphoric attention, a susceptibility to attentional capture by negative events. Neurally, this

model is characterized by elevated activity in the amygdala, anterior insula and anterior cingulate cortex, and attenuated activity in the dorsolateral prefrontal cortex (DLPFC) (Drevets, Savitz, & Trimble, 2008; Hamilton et al., 2012; Siegle, Thompson, Carter, Steinhauer, & Thase, 2007). Heightened amygdala activity is the most prototypical VF of dysphoric attention, having been detected both metabolically through PET imaging and functionally through fMRI-derived responses to negative stimuli. Indeed, amygdala hyperarousal in depressed individuals persists even after negative emotional stimuli are no longer present (Siegle et al., 2007).

One of the amygdala's primary functions is to enable the rapid orienting of attention to motivationally-salient stimuli (Vuilleumier, 2005), a capacity which is biased towards negative information during acute episodes of depression (Gotlib, Krasnoperova, Yue, & Joormann, 2004). Habitual dysphoric attention creates a negatively-skewed context for appraisals of subjective well-being, and accordingly metabolic rate in the right amygdala predicts negative mood in depressed patients (Abercrombie et al., 1998). Conversely, one proposed mechanism of ADMs is that they promote a positive bias in attention to counter dysphoric attention (Harmer & Cowen, 2013). While amygdala reactivity to negative stimuli often normalizes following successful ADM (Arnone et al., 2012; Sheline et al., 2001) or CT (Fu et al., 2008), elevated amygdala reactivity is still observed in remitted patients following negative mood challenge and is associated with dysphoric attention and memory biases (Ramel et al., 2007).

The amygdala does not operate in isolation. In healthy individuals, the amygdala response to negative stimuli is regulated by dorsal and ventral aspects of the prefrontal cortex (PFC). For example, the act of labeling emotional facial expression relative to other characteristics such as gender (Lieberman et al., 2007) promotes ventral PFC activation and a commensurate reduction in amygdala activity. In individuals who suffer from MDD, the ability to regulate negative information is compromised, as evidenced by disrupted connectivity between the PFC and amygdala (Heller et al., 2009; Johnstone, van Reekum, Urry, Kalin, & Davidson, 2007). Relative to healthy controls, remitted MDD patients demonstrate reduced rostral anterior cingulate and dorsomedial PFC activation in response to task feedback on a response inhibition (Go/No-Go) paradigm, commensurate with reduced executive recruitment even in the face of performance errors (Nixon, Liddle, Worwood, Liotti, & Nixon, 2013). Reduced DLPFC reactivity to dysphoric stimuli is also associated with high levels of hopelessness (Zhong et al., 2011), potentially reflecting habituation to repeated failures to redirect attention. Consistent with its characterization as a residual symptom marker, DLPFC normalization is associated with depressive symptom resolution following both ADM (Schaefer, Putnam, Benca, & Davidson, 2006) and CT (Brody et al., 2001). Sustained DLPFC hypoactivity in remission is therefore an additional neural indicator of dysphoric attention.

Neural Mechanisms of Dysphoric Elaboration

Neurally, dysphoric elaboration can be framed in terms of habitual engagement in an analytic or evaluative mode of processing, particularly in response to emotional stress. As such, the neural predictions for dysphoric elaboration are contrary to that of dysphoric

attention: greater PFC activity is expected when such self-referential elaboration is triggered, compared to reduced activation commonly observed during dysphoric attention to external stimuli. Which of these patterns is evident may depend on experimental paradigms, with unconstrained responses to mood challenge promoting analytic self-focus (and hence PFC activation) compared to PFC engagement failures during externally-directed experimental tasks. Consistent with this account, rumination about the self may be characterized by elevated rather than reduced PFC stress reactivity. For example, people high in rumination show elevated PFC activity when directing attention away from dysphoric stimuli (Chuen Yee Lo, Lau, Cheung, & Allen, 2012; Diener, Kuehner, Brusniak, Struve, & Flor, 2009), potentially reflecting the difficulty of disengaging from habitual elaborative processes.

Emerging findings have begun to implicate the medial PFC as the primary neural correlate of dysphoric elaboration. Elevated medial PFC activity has been observed during self-referential processing in depression (Lemogne et al., 2009) and in response to mood challenge in both subclinical (Farb et al., 2010) and remitted patients (Farb, Anderson, Bloch, & Segal, 2011). While decreased DLPFC activity may be a marker for MDD that normalizes with symptom remission (Brody et al., 2001; Siegle et al., 2007; Zhong et al., 2011), the medial PFC continues to display elevated stress reactivity (Lemogne et al., 2010) and resting-state connectivity (Li et al., 2012). Similarly, ADM reduces medial PFC reactivity to negative self-descriptors in individuals at high risk for MDD (Di Simplicio, Norbury, & Harmer, 2012), but medial PFC reactivity to mood challenge persists in medicated, remitted patients, with reactivity in this region predicting future relapse/recurrence (Farb et al., 2011).

Vulnerability factors as interacting neural systems

On a neural level, sensitization occurs because of increased coupling between brain networks that support dysphoric attention and elaboration, which together elevate relapse/recurrence risk with each episode experienced. This elevated risk may be the product of interacting brain networks, sets of intrinsically correlated brain regions that are each normally associated with a different form of information processing (Figure 2). In accordance with the coupling-as-vulnerability prediction of the two-factor model, a central finding in network studies of MDD is the conflation of multiple mental processes into a common ruminative cycle. Normally, the prefrontal lobe hosts three distinct networks, including the ‘task-independent’ default mode network (DMN), the ‘task-positive’ executive network (EXN), and the ‘task-switching’ network sensitive to affective salience (SLN) (Menon & Uddin, 2010; Seeley et al., 2007). In MDD these networks are simultaneously activated in the dorsal MPFC (Sheline, Price, Yan, & Mintun, 2010), interfering with the resolution of dysphoric cognition. The consequence of this conflation is that automatic appraisals of affective salience and subsequent conceptual elaboration interfere with efforts to adaptively direct attention and behavior.

Of the three networks, the DMN has been most consistently linked to MDD; its activation during task-irrelevant, internally directed thought (Mason et al., 2007) is consistent with a theory of habitual elaboration disrupting regulatory efforts. Evidence for DMN hyperactivity

is apparent in remission from MDD, both in terms of elevated functional connectivity and hypogyrification of the DMNs central hub in the precuneus and posterior cingulate of the brain (Nixon, Liddle, Nixon, et al., 2013). Consistent with its hypothesized relationship to dysphoric elaboration, the prefrontal hub of the DMN has been associated with elaborative self-referential processing in depression (Lemogne, Delaveau, Freton, Guionnet, & Fossati, 2012). Furthermore, the prefrontal DMN has shown exaggerated connection strength and diffuseness in MDD (Sheline et al., 2009), failing to deactivate during cognitively demanding tasks, which may indicate interfering rumination (Lemogne et al., 2012).

In parallel, progressive EXN dysfunction associated with dysphoric attention may help to explain why DMN processing is able to dominate dorsal nexus activity. The DLPFC is one of the principal nodes of the EXN, and is associated with control over visceral impulses (Baumgartner, Knoch, Hotz, Eisenegger, & Fehr, 2011) and adaptive emotion regulation (Goldin, McRae, Ramel, & Gross, 2008), empowering goal-directed behavior (Ballard et al., 2011). However, DLPFC regulatory capacity may be compromised by acute stress (Qin, Hermans, van Marle, Luo, & Fernandez, 2009). Rather than lying dormant, DLPFC activity appears to become co-opted into ruminative processes during both MDD episode and remission (Cooney, Joormann, Eugene, Dennis, & Gotlib, 2010; Farb et al., 2011), contributing to findings of diffuse DMN activity in depression (Sheline et al., 2009). Accordingly, higher DLPFC activity during self-referential processing has been associated with lower rates of remission in MDD (Lemogne et al., 2010). Similarly, higher DLPFC activity during emotional tasks has been linked to increased depression severity and feelings of hopelessness (Grimm et al., 2009).

Our discussion of neural networks has focused primarily on the presence of dysphoric elaboration and the absence of cognitive control in dysphoric attention. However, dysphoric attention manifests as an attentional bias driven both by elevated DLPFC reactivity (Kerestes et al., 2012), and recruitment of the third dorsal nexus network, the SLN, which includes the amygdala, a structure prominent in dysphoric attention. The SLN is involved in the redirection of attention towards emotionally salient stimuli (Seeley et al., 2007), which is characterized by anterior right insula activation (Menon & Uddin, 2010). In MDD, anterior insula activation occurs most often following high levels of EXN activity, indicating a tendency to switch to DMN rumination, whereas in healthy controls, insula activation follows high levels of DMN activity, indicating a habit of disengaging from rumination and getting back to the task at hand (Hamilton et al., 2011).

The ability to flexibly allocate attention via the SLN may be important for sustained well-being. When attention is constructively engaged, as in a guided breathing exercise, trait non-reactivity is associated with reduced insula switch-signals to emotional stimuli and better task performance (Paul, Stanton, Greeson, Smoski, & Wang, 2013). Conversely, following emotional challenge, trait rumination is linked to increased insula switch-signals, consistent with the prioritization, and consequently attention, to negative or unexpected events. Such attention may then facilitate further dysphoric elaboration. Thus, the co-activation of these three networks is associated with rumination, compromised cognitive control, and redirection of attention to dysphoric information that further reinforces ruminative patterns (Figure 2). Such co-activation resonates with the two-factor model's sensitization prediction

of increased coupling between dysphoric attention and dysphoric elaboration. Within this reactive cycle, vulnerability may be characterized by event interpretation that is prejudiced by habitual expectations: in a study of remitted patients, prefrontal hyperactivity has been observed during reward anticipation, relative to SLN hypoactivation observed during reward outcomes (Dichter, Kozink, McClernon, & Smoski, 2012). Thus, habitual expectations may begin to dominate perception, whereas actual outcomes are met with an attenuated prefrontal response.

It would be reasonable to infer from this research that DMN activity is inherently maladaptive, representing a withdrawal from the external world and goal-directed cognition (e.g., Marchetti, Koster, Sonuga-Barke, & De Raedt, 2012). However, it is important to recall that dysphoric elaboration is defined as engagement of an analytic *process* with dysphoric *content*. From this perspective, DMN activity represents only the analytic process, which is not in itself adaptive or maladaptive. Indeed, a comparison of EXN and DMN activity over time suggests no differences in the ratio of network dominance between MDD and healthy controls (Hamilton et al., 2011). However, in people with a history of depression, DMN dominance correlates with higher levels of depressive rumination (Berman et al., 2011; Hamilton et al., 2011). Prospective clinical research corroborates this process/content interaction: rumination predicts depressive symptoms, but only following the dysphoric content introduced by negative life events (Abela, Hankin, Sheshko, Fishman, & Stolow, 2012). Similarly, negative cognitive style, the tendency to generate global negative thoughts, interacts with rumination to predict the incidence, number and duration of future depressive episodes, while rumination alone is not predictive when the interaction term is included in the model (Robinson & Alloy, 2003).

Thus, DMN hyperconnectivity may indicate relapse/recurrence sensitization insofar as it reflects conflation between dysphoric attention (SLN/EXN) and elaboration (DMN) processes. In such situations, reducing DMN activity may have prophylactic benefits. Adults with early life stress but without psychiatric illness have demonstrated reduced DMN connectivity compared to healthy controls (Philip et al., 2013), suggesting that avoiding the process of self-referential rumination may be a stress coping mechanism. One mechanism by which Ketamine, an NMDA antagonist with antidepressant properties, may exert its effects is by decoupling DMN connectivity with the dorsal nexus (Scheidegger et al., 2012). Cognitive therapy may increase subgenual cingulate and MPFC reactivity to positive stimuli while attenuating reactivity to negative stimuli, a neural activity change that accounts for reductions in depressive symptoms (Yoshimura et al., 2013). Thus, reductions in vulnerability may be assessed by the extent to which networks for attention, executive control, and elaboration are rendered more distinct, commensurate with decoupling of dysphoric attitudes and elaboration.

Concluding Remarks

Existing research supports a two-factor model of sensitization in recurrent depression, predicated on dysregulation in the cognitive domains of attention and elaboration. Based on the established contribution of both dysphoric attention and elaboration to depressive affect, the model predicts that fixation on negative features of life events and subsequent dysphoric

rumination serve as a mutually reinforcing cognitive pattern, a pattern strengthened through repeated association during depressive episodes. The product of such rehearsal is sensitization to adverse life events, as even relatively minor features of adverse experience are fixated upon and allowed to trigger powerful dysphoric elaborations about the self, future, and world.

The idea that the coupling of dysphoric attention and elaboration promotes a more chronic illness course is a largely untested but empirically tractable claim, as the impact of these two VFs has been established independently but rarely measured in tandem. If the two factor account can be validated, the interaction between dysphoric attention and elaboration would offer a plausible account for sensitization effects in unipolar mood disorder. If future validation studies produce positive findings, the two-factor model may aid in the identification of remitted patients who would be best matched to targeted therapies, thereby increasing effective MDD prevention.

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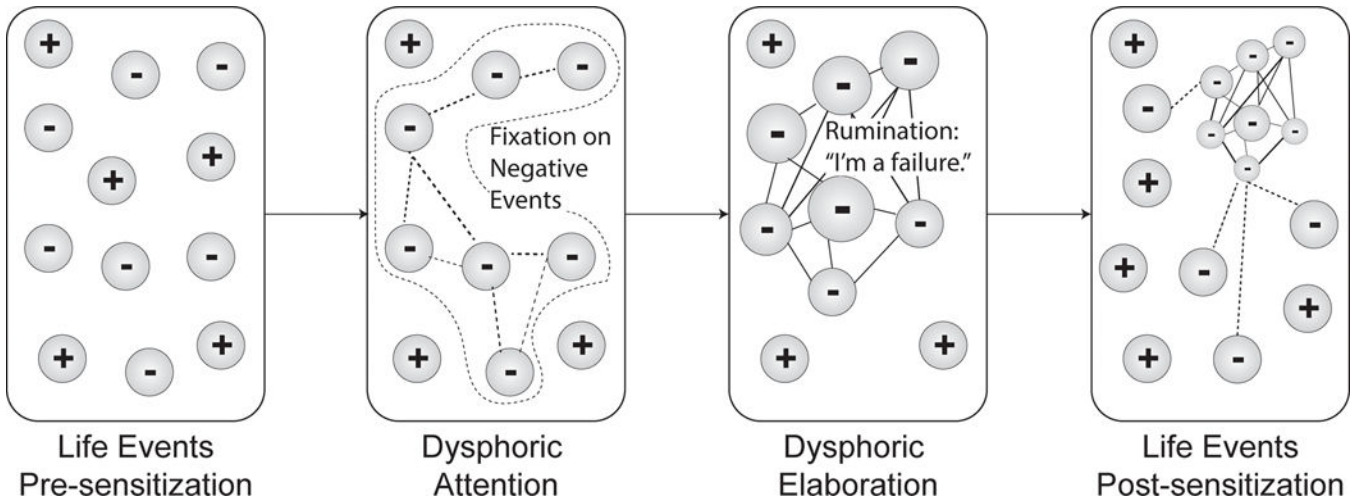


Figure 1. Introducing the two-factor model of depression vulnerability. Subjective experience is presented in each rounded rectangle, reflecting the dynamic process of sensitization over time. Experience is constituted by both positive (+) and negative (-) events, which are dynamically modified by cognition. Weak associations are illustrated as dotted lines and strong associations by solid lines.

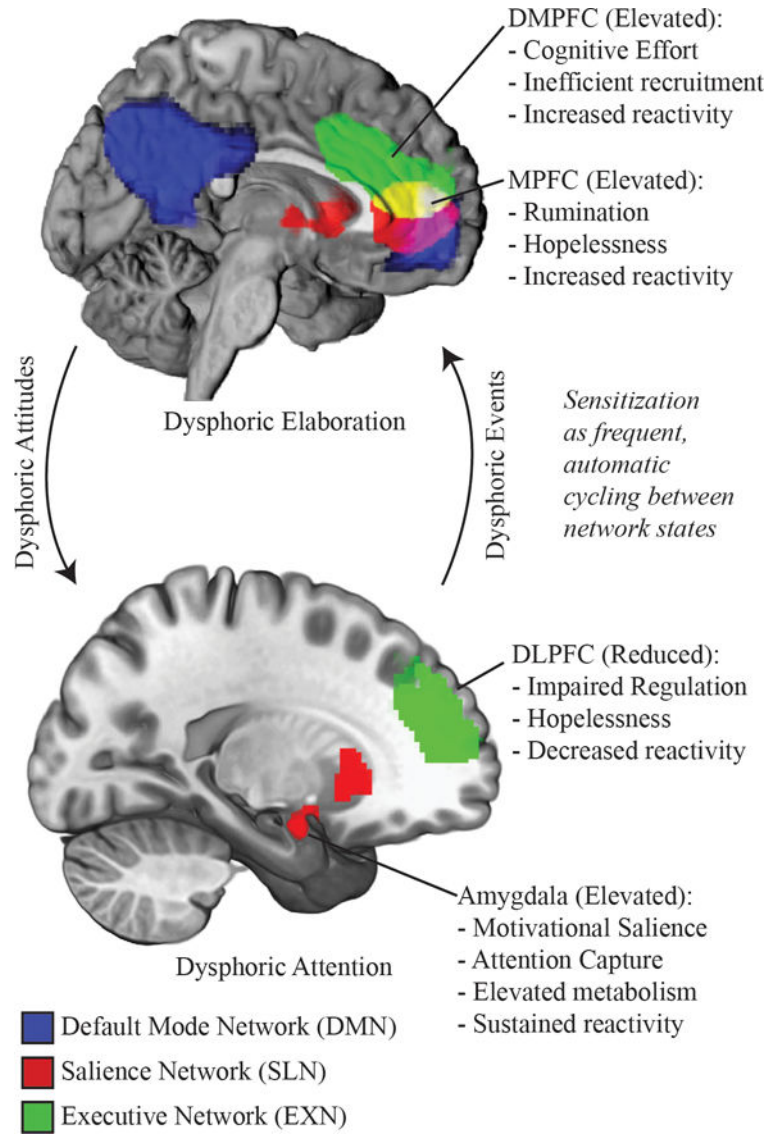


Figure 2. A schematic of the 3 intrinsically-connected networks associated with depression vulnerability. Dysphoric attention is characterized by increased salience network (SLN) and reduced executive network (EXN) activity. Prolonged attention to dysphoric content may promote dysphoric elaboration, co-opting EXN function into habitual self-evaluation and elaboration characteristic of the default mode network (DMN). Dysphoric elaboration may in turn create dysphoric expectations, biasing selection and maintaining dysphoric attention.

Table 1

Candidate methods for assessing dysphoric attention and dysphoric elaboration.

Task Name	Description	Vulnerability Marker
<i>Dysphoric attention</i>		
Dot Probe	Present emotional and neutral word simultaneously for > 1 sec, then replace with target 'dot' behind one of the words.	Sensitivity as reaction time to negative vs. neutral words (Fritzsche et al., 2010); bias only visible at longer presentation time might indicate combined attention / elaboration components.
Emotional Stroop	Record time for reading emotional vs. neutral words printed in different colors.	Sensitivity as reaction time to negative vs. neutral words (Williams, Mathews, & MacLeod, 1996)
Spatial Cueing	Cue 1 of 2 spatial locations with either a neutral or negative word or image; cue either rightly or wrongly predicts target location.	Sensitivity as greater effect of cue validity for negative vs. neutral words (Leyman et al., 2007).
Eye Tracking	Naturalistic viewing of neutral and dysphoric photographs.	Sensitivity as greater fixation time to dysphoric images (Caseras et al., 2007).
Neuroimaging	fMRI analysis of negative vs. neutral stimulus presentation.	Sensitivity as greater amygdala and attenuated DLPFC response to negative images (Ramel et al., 2007).
<i>Dysphoric elaboration</i>		
Negative Self-Ideation	Compare endorsement of dysphoric self-descriptors before and after negative mood induction.	Reactivity as elevation of dysphoric self-descriptors (Segal, Gemar, & Williams, 1999); in situations where elevation is not apparent, negative mood elevation or high baseline self-ideation may also serve as risk predictors (van Rijsbergen et al., 2013).
Scrambled Sentence Completion	Create either positively or negatively valenced sentences from scrambled words.	Negative completion trend predicts MDD symptoms (Rude, Wenzlaff, Gibbs, Vane, & Whitney, 2002) and future diagnosis (Rude, Durham-Fowler, Baum, Rooney, & Maestas, 2010).
Dysfunctional Attitudes	Compare endorsement of dysphoric attitudes before and after negative mood induction.	Extended Attributional Style Questionnaire (Peterson & Villanova, 1988) assesses global cause attribution, and the Cognitive Style Questionnaire (Abramson & Metalsky, 1986) assesses attitudes about future and the self. Dysfunctional Attitudes Scale assesses negative thinking patterns (Segal et al., 2006).
Avoidance of Negative Affect	Assess self-reported acceptance of negative emotion and ability to nonjudgmentally observe thoughts.	Reactivity as low levels of self-endorsed acceptance or decentering (Bieling et al., 2012).
Neuroimaging	Compare neural reactivity between neutral and dysphoric film clips.	Reactivity as elevated medial prefrontal and reduced sensory cortex activation during sad film viewing (Farb et al., 2011).

Note: see De Raedt & Koster (2010) for a different review of attentional paradigms in depression.

Table 2

A summary of the claims and prediction of the two-factor model of sensitization in depression vulnerability.

Claim / Prediction	Key Evidence	Future Questions
1) Vulnerability operates at concrete and implicational levels of processing	<ul style="list-style-type: none"> - Dysphoric attitudes and life events independently predict depressive symptoms (Smith et al., 1985). - Negatively biased attention is apparent in acute and remitted MDD (Caseras et al., 2007; Fritzsche et al., 2010; Leyman et al., 2007). - Cognitive reactivity is heightened in acute and remitted MDD (Ingram et al., 2011; Jeanne et al., 1998; Teasdale & Cox, 2001) and predicts relapse (Segal et al., 2006). 	<ul style="list-style-type: none"> - Does dysphoric attention predict relapse vulnerability?
2) Processing biases are malleable	<ul style="list-style-type: none"> - Dysphoric attention can be modified (MacLeod et al., 2002; Wells & Beevers, 2010). - Dysphoric elaboration can be modified (Hallion & Ruscio, 2011; Ma & Teasdale, 2004). 	<ul style="list-style-type: none"> - What interventions are most efficacious for bias modification?
3) Attention and schematic biases have independent tuning mechanisms	<ul style="list-style-type: none"> - Affect-biased attention regulates emotion (Todd et al., 2012; Wadlinger & Isaacowitz, 2011). - Induced rumination impairs cognition and mood (Gilbert & Gruber, 2014; Guastella & Moulds, 2007; Watkins & Teasdale, 2001; Yoon & Joormann, 2012). - Fixation and rumination are fairly independent (Donaldson et al., 2007; Joormann, 2006; Joormann et al., 2006; Joormann & Gotlib, 2008). 	<ul style="list-style-type: none"> - How do fixation and rumination change over the lifespan? - How do changes in one mechanism impact on risk of episode return when both VFs are included in a predictive model?
4) Fixation and rumination have mutually reinforcing effects	<ul style="list-style-type: none"> - Rumination mediates the relationship between fixation and depressive symptoms in both clinical and subclinical MDD (Everaert et al., 2014; Everaert et al., 2013). - Remitted MDD patients show negative appraisal of ambiguous neutral stimuli (Bhagwagar et al., 2004; Leppanen et al., 2004). 	<ul style="list-style-type: none"> - Is the fixation / rumination relationship circular or linear? - What are the tuning consequences of fixation on dysphoric elaboration and rumination on dysphoric attention?
Prediction: MDD sensitization involves fixation causing rumination	<ul style="list-style-type: none"> - High rumination in children predicts greater depressive symptoms in response to life stress (Abela & Skitch, 2007). - Dysphoric elaboration rather than attention is the central predictor of relapse risk (Halvorsen et al., 2010). 	<ul style="list-style-type: none"> - Does tracking both VFs simultaneously improve prediction of relapse/recurrence risk? - Does dysphoric attention increase MDD vulnerability through a path mediated by dysphoric elaboration?