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Review

Depression: A repair response to stress-induced neuronal microdamage that can grade into a chronic neuroinflammatory condition?

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ABSTRACT

Depression is a major contributor to the global burden of disease and disability, yet it is poorly understood. Here we review data supporting a novel theoretical model for the biology of depression. In this model, a stressful life event leads to microdamage in the brain. This damage triggers an injury repair response consisting of a neuroinflammatory phase to clear cellular debris and a spontaneous tissue regeneration phase involving neurotrophins and neurogenesis. During healing, released inflammatory mediators trigger sickness behavior and psychological pain via mechanisms similar to those that produce physical pain during wound healing. The depression remits if the neuronal injury repair process resolves successfully. Importantly, however, the acute psychological pain and neuroinflammation often transition to chronicity and develop into pathological depressive states. This hypothesis for depression explains substantially more data than alternative models, including why emerging data show that analgesic, anti-inflammatory, pro-neurogenic and pro-neurotrophic treatments have antidepressant effects. Thus, an acute depressive episode can be conceptualized as a normally self-limiting but highly error-prone process of recuperation from stress-triggered neuronal microdamage.

Contents

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1. Introduction

Depression is projected to become the second biggest contributor to the global burden of disease and disability by the year 2020 (World Health Organization, 2009), yet significant unmet need for treatment exists (Greden, 2002). Studies that have used modern techniques to assess depressive episodes in the general population concur that 13–16% of adult United States residents meet criteria for having experienced Major Depressive Disorder so far in their lives (Hasin et al., 2005; Kessler et al., 2003), perhaps reaching 20% when extrapolated to the entire lifespan. In these general population samples, the average depressive episode is 3 or 4 months in duration (Eaton et al., 2008; Kessler et al., 2003; Spijker et al., 2002). About half of the first time sufferers will recover and never experience a recurrence (Eaton et al., 2008), although approximately 20% of depressive episodes run a chronic course lasting two years or longer (Spijker et al., 2002). These data reveal that depression in the general population, almost half of which is left untreated (Eaton et al., 2008; Hasin et al., 2005; Kessler et al., 2003), is more common, briefer in duration, and less often recurrent than is apparent from studies of clinical samples.

In this article, we review findings that shape our understanding of the biology of depression, including that depression is often triggered by stressful life events (Section 2), that stress triggers neuronal microdamage (section 3) and neuroinflammatory activation (Section 4) in the brain, and that inflammatory mediators can induce depressive symptoms (Section 5). In addition, we review evidence that anti-inflammatory treatments are emerging as having antidepressant effects (Section 6) and that antidepressant treatments increase neurogenesis, neurotrophins and neuronal plasticity (Section 7). By utilizing these findings in diverse ways, a variety of theoretical models (reviewed in Section 8) have proposed that different malfunctions lead to depression. However, no single view has garnered a widespread consensus, leaving the field without a unified theoretical framework that organizes the disparate findings and guides future research.

Because it is difficult to understand *dysfunction* of any process without an appreciation of what the *healthy functioning* of the process is, our approach in Section 9 is to use these same findings to elaborate a theoretical model for the proper biological functioning of the response to stressful events. In this theoretical model, a healthy response to stress-induced neuronal microdamage consists of an injury repair process with inflammatory-mediated demolition and stem cell-facilitated regrowth. The inflammatory mediators create an episode of psychological pain and sickness behavior which comprise depressive symptoms. In using this injury repair model to refine existing hypotheses about pathology in depression, we suggest in Section 10 that this normally self-limiting repair response may become chronic or exaggerated by similar mechanisms to those that commonly lead to chronic inflammatory and pathological pain conditions.

Implications of this brain injury repair model for depression are discussed in Section 11. For example, because our theoretical model invokes physical pain mechanisms for psychological pain, it offers biological scenarios explaining why analgesics appear to have some antidepressant effects, and why depression shares features with a family of disorders involving central sensitization of pain pathways and hyperalgesic priming. Because our theoretical model proposes that depressive symptoms are a result of inflammatory mediators released during repair of stress-induced brain injury, it offers an explanation for why brain injury induced by means other than stress also results in depression at a high rate. Regarding drug discovery, this model underscores that brain injury, neuroinflammation, and pain mechanisms may represent therapeutic targets for depression. We propose the additional hypotheses that a function accomplished during the acute depressive episode is to dismantle neural circuitry underlying behavior that has been rendered disadvantageous by the life event and to grow neural tissue mediating new behavioral strategies (Section 11.2); and that the degree of depressogenicity of the stressor is related to the extent, type and neuroanatomical location of the remodeling (Section 11.3). Finally, we suggest that the graded nature of the response can explain the common sense notion that depression is on a continuum with normal sadness.

A note about terminology: The criteria by which a typical reaction to a harrowing event or environment is distinguished from a mental "disorder" is the topic of much controversy, e.g. (Kendler et al., 2008; Maj, 2008; Wakefield et al., 2007). Therefore, throughout this review, we will use the general terms "depression" and "depressive episode" to refer to the full range of severity of depressive symptoms, including both those that do and do not reach the DSM-IV-TR (American Psychiatric Association, 2000) criteria for "Major Depressive Disorder" and "Major Depressive Episode".

2. Data suggest that stressful life events can precipitate depressive episodes in humans

An association between stressful life events and depressive episodes has long been noted (Hammen, 2005; Paykel, 2001) (for reviews). The onset of the first episode of depression is preceded by a severe life event in 70–80% of cases (Brown et al., 1986, 1995; Kendler et al., 1999). To address causality, some studies have focused on events that are judged to be "bad luck" or "fateful" to exclude events that might have been brought on by the person's own potential prodromal dysfunction. The odds that a person with major depression has experienced a disruptive, fateful event have been measured at 2.5 times that of community residents who have no apparent depression (Shrout et al., 1989). In a separate study, events judged to have not resulted from the patients own behavior strongly predicted the occurrence of an onset of major depression at an odds ratio of 2.33 (Kendler et al., 1999). In populations subject to mass conflict and displacement in which the number of potentially traumatic events experienced was positively associated with depression, time since conflict was negatively associated (Steel et al., 2009) (for meta-analysis). These findings support the notion that causality can flow from the stressful event to the depressive episode.

Examples of depression-associated stressors include physiological and psychological events, such as transitioning to menopause (Cohen et al., 2006; Freeman et al., 2004, 2006), experiencing major health problems such as myocardial infarction (Ziegelstein, 2001) (for review), having a baby (Paulson and Bazemore, 2010) (Robertson et al., 2004) (for review), and caregiving for a loved one with degenerative disease (Mahoney et al., 2005).

Simple, one-way causality is not the whole story, however. Stressful life events may also be a consequence of depression. Supporting this possibility, people with a history of depression are significantly more likely, even in periods of remission, to experience high levels of subsequent episodic life events to which they themselves contributed (Hammen, 2005) (for review). Causality may sometimes run bidirectionally, as has been suggested for the myocardial infarction–depression link (Lippi et al., 2009) (for review). While life events can be both a cause and consequence of depression, causality may also come from a third factor. Supporting this possibility, people who are high on the personality trait of neuroticism are at greater overall risk of major depression and are more sensitive to the depressogenic effects of adversity (Kendler et al., 2004). Furthermore, causality may shift over the course of the illness. This contention is supported by the finding that first episodes of depression are more strongly associated with major life stress than subsequent episodes, which has led to a kindling hypothesis (Kendler et al., 2000) (Monroe and Harkness, 2005) (for review). Finally, not all stressful life events elicit depression in all people each time such an event occurs (Bonanno, 2004).

Therefore, stressful life events and depression likely share a complex relationship. Within this complexity, however, the most recent review of the field concludes that overall, the evidence indicates that a robust proportion of the association is due to causality flowing in the direction of the event to depression (Hammen, 2005) (for review). Establishing this type of causality is important for developing a theoretical model of depression because it suggests that stress can initiate a cascade of biological events that lead to depression.

3. Stress can trigger remodeling and microdamage in the brain

> *"... one is ... an unwilling witness of an execution, the disintegration of one's own personality ... this phase comes to a dead-end, eventually, and is succeeded by vacuous quiet. In this you can try to estimate what has been sheared away and what is left"* (Fitzgerald, 1996) describing a depressive episode he had experienced.

A finding that has emerged with particular clarity over decades of research is that stress reshapes the physical structure of the brain (Arnsten, 2009; Lupien et al., 2009; McEwen, 2007; Rodrigues et al., 2009) (for reviews). Stress triggers increases in markers of apoptosis (Bachis et al., 2008; Jalalvand et al., 2008; Lucassen et al., 2001), decreases in neurogenesis (Alonso et al., 2004; Bain et al., 2004; Bland et al., 2006; Chen et al., 2006a; Cherng et al., 2010; Czeh et al., 2001, 2002, 2007; Dagyte et al., 2009; Ferragud et al., 2010; Goshen et al., 2008; Gould et al., 1997; Heine et al., 2004; Hill et al., 2006; Koo and Duman, 2008; Lagace et al., 2010; Lee et al., 2006a; Luo et al., 2005; Malberg and Duman, 2003; Oomen et al., 2007; Pham et al., 2003; Rosenbrock et al., 2005; Thomas et al., 2007; Torner et al., 2009; Westenbroek et al., 2004; Xu et al., 2006a; Zhou et al., 2007) but see (Parihar et al., 2010), and region-specific changes in brain derived neurotrophic factor (BDNF), both increases (Aguilar-Valles et al., 2005; Berton et al., 2006; Bland et al., 2005, 2007; Charrier et al., 2006; Dagnino-Subiabre et al., 2006; Givalois et al., 2001, 2004; Hammack et al., 2009; Lee et al., 2006b; Li et al., 2007; Marmigere et al., 2003; Molteni et al., 2009; Pardon et al., 2005; Rage et al., 2002; Schulte-Herbruggen et al., 2009) and decreases (Adlard and Cotman, 2004; Aleisa et al., 2006; Bland et al., 2007; Cavus and Duman, 2003; Charrier et al., 2006; Chen et al., 2008b; Duric and McCarson, 2005, 2006; Dzitoyeva et al., 2008; Fuchikami et al., 2009; Gronli et al., 2006; Kozlovsky et al., 2007; Li et al., 2009; Luo et al., 2004; Murakami et al., 2005; Park et al., 2009; Scaccianoce et al., 2003; Smith et al., 1995; Takeda et al., 2006; Vaidya et al., 1999; van Donkelaar et al., 2009; Vollmayr et al., 2001; Xu et al., 2002, 2004, 2006a,b; Yun et al., 2002), with a minority of studies detecting no change (Allaman et al., 2008; Lucca et al., 2008).

In studies that have directly examined neuronal structure, stress was found to induce neurite *growth* in certain brain regions, e.g. (Dias-Ferreira et al., 2009; Liston et al., 2006; Vyas et al., 2002). However, many more studies have documented that stress leads to a *reduction* of dendritic, spine, and synaptic material in the hippocampus and prefrontal cortex. Some studies have referred to this morphological change with stress as "atrophy", e.g. (Conrad et al., 1999; Galea et al., 1997; Lambert et al., 1998; Liu and Aghajanian, 2008; Magarinos and McEwen, 1995a, 1995b, Magarinos et al., 1996; Ramkumar et al., 2008; Watanabe et al., 1992a, 1992b). Some have called it "retraction", e.g. (Conrad, 2006; Izquierdo et al., 2006; McLaughlin et al., 2005, 2010; Radley et al., 2005). Some call it "loss", e.g. (Chen et al., 2008c; Radley et al., 2006; Sandi et al., 2003). Others have used the term "damage", e.g. (McEwen and Magarinos, 2001; McEwen, 2002; Sapolsky, 1996; Sousa et al., 2000; Sunanda et al., 1997). For the purposes of this review, we will refer to the stress-induced reduction of neuronal material as "microdamage".

Most studies addressing structural change with stress have used chronic stress protocols, but structural changes have also been observed after brief stressors. For example, in the hippocampus, a reduction in dendritic spines can be seen within hours of either the onset of restraint stress (Chen et al., 2008c) or intermittent tail-shock (Shors et al., 2001), and brief social defeat stress induces a reduction in apical dendritic length (Kole et al., 2004). Loss of dendritic length has also been seen in the infralimbic cortex after a single ten minute episode of swim stress (Izquierdo et al., 2006).

These structural changes can be transient. After cessation of stress, some replacement of missing tissue can be observed within 30 days (Conrad et al., 1999; Goldwater et al., 2009; Radley et al., 2005; Sousa et al., 2000). The stress-induced loss of neuronal material can be reversed more quickly if a new learning (Sandi et al., 2003) or rewarding (Ramkumar et al., 2008) experience is provided, suggesting that learning and reward counter the effects of stress on brain structure.

Structural changes are also seen in the brains of depressed patients (Ebmeier et al., 2006) (for review). The best studied change is reduced hippocampal volume, which has been confirmed in three meta-analyses (Campbell et al., 2004; McKinnon et al., 2009; Videbech and Ravnkilde, 2004). The reduced hippocampal volume in depression may not be apparent if the duration of illness is less than two years or fewer than two episodes (McKinnon et al., 2009) (for meta-analysis). This volume loss is significantly positively correlated with the total number of previous episodes (Videbech and Ravnkilde, 2004 for meta-analysis). Thus, the data suggest that the reduced volume generally occurs after disease onset (McKinnon et al., 2009) and may be a consequence of repeated episodes of depression (Videbech and Ravnkilde, 2004). In addition, there is also evidence that among people who have familial risk of depression but have not yet had a first episode, some hippocampal volume decrease preexists (Baare et al., 2010; Chen et al., 2010a; Rao et al., 2009). In a recent review analyzing various possible explanations for the hippocampal volume decrease in depression, alterations in dendritic, axonal, and synaptic components, as well as putative glial changes were considered to be more consistent with the data (including postmortem analyses) than massive neuronal loss or a suppression of neurogenesis. However, shifts in fluid balance or changes in the extracellular space could not be excluded (Czeh and

Lucassen, 2007) (for review). Some evidence suggests that effective antidepressant treatment reverses hippocampal volume changes (Ebmeier et al., 2006) (for review).

Thus, a picture is emerging that stress can induce structural remodeling including reversible microdamage in the rodent brain, a phenomenon that may be echoed in human depression. Even brief stressors have been found to elicit such structural change in the rodent.

4. Stress may stimulate the neuroinflammatory system

Evidence of inflammatory activation can be observed in both blood and brain of stressed rodents and humans. For example, acute stress increases markers of inflammation in the blood circulation of rodents, e.g. (Grippo et al., 2005; Hale et al., 2003; Johnson et al., 2005). Stress induces cytokine responses in various rodent brain regions, e.g. (Barnum et al., 2008; Blandino et al., 2006, 2009; Goshen et al., 2008; Grippo et al., 2005; Johnson et al., 2005; Kwon et al., 2008; Murray and Lynch, 1998; Nguyen et al., 1998) (Garcia-Bueno et al., 2008; Munhoz et al., 2008) (for reviews). Although there have been inconsistencies across studies, these may be attributed to varying stressor characteristics (Deak et al., 2005a,b) and to regional selectivity in the response to a given stressor (Blandino et al., 2009). In addition to cytokine responses, both acute and chronic stress induce inflammatory signs in microglia (the resident inflammatory cells of the brain) such as increases in microglial proliferation (Nair and Bonneau, 2006), morphological activation (Sugama et al., 2007, 2009), activation marker expression (Frank et al., 2007), and decreases in a marker of microglial quiescence (Blandino et al., 2009) in various brain regions. In addition, stress increases the number of microglia in certain stress-sensitive brain regions and triggers a marked transition of microglia from a ramified-resting state to a non-resting state (Tynan et al., 2010). There is even one report of recruitment of bone-marrow derived cells into the hippocampus during stress (Brevet et al., 2010), suggesting that stress may trigger full blown neuroinflammation rather than merely activating brain cytokine signaling. Treatment with the putative microglial inhibitor minocycline prevented the stress-induced rise in interleukin (IL)-1 expression (Blandino et al., 2006, 2009), suggesting that the stress-induced activation of microglia may be responsible for some of the cytokine responses. In humans, acute stress induces a robust increase in inflammatory cytokines IL-6 and IL-1 in the blood circulation (Steptoe et al., 2007) (for review and meta-analysis). In addition, one study found elevated levels of the inflammatory mediator substance P in cerebrospinal fluid of stressed human subjects (Geracioti et al., 2006).

In depressed patients, many, but not all studies have found signs of inflammatory activation in the blood circulation. Three recent meta-analyses (Dowlati et al., 2009; Howren et al., 2009; Zorrilla et al., 2001) concur that overall, the data support the conclusion that the hallmarks of inflammatory activation are present in the blood circulation of depressed subjects. Evidence for altered levels of inflammatory mediators in cerebrospinal fluid of depressed patients has been inconsistent, e.g. (Carpenter et al., 2004; Deuschle et al., 2005; Geracioti et al., 2006; Levine et al., 1999; Lindqvist et al., 2009).

Note that the presence of inflammatory markers in the blood circulation does not necessarily indicate a peripheral site for the inflammation because activation of the resident inflammatory system within the brain also results in inflammatory markers in the blood. For example, elevations of circulating cytokines occur in other disorders with solely central nervous system (CNS) inflammation, such as Alzheimer's disease (Alvarez et al., 2007; Bonotis et al., 2008; De Luigi et al., 2002; Licastro et al., 2000; Lombardi et al., 1999; Sala et al., 2003; Zuliani et al., 2007) and stroke (Allard et al., 2004; Castellanos et al., 2004; Di Napoli et al., 2001; Intiso et al., 2004; Lynch et al., 2004; Pedersen et al., 2004; Reynolds et al., 2003; Rost et al., 2001; Silvestri et al., 2004; Smith et al., 2004).

Taken together, the studies reviewed in this section suggest that stress elicits evidence of inflammatory activation in the rodent brain with inflammatory signs in the blood circulation of stressed and depressed people. The mechanism by which stress might induce neuroinflammatory responses is not yet clear. It has been suggested that inflammatory activity in the brain is induced, paradoxically, by the usually anti-inflammatory glucocorticoids that are released during stress (Sorrells and Sapolsky, 2007) (for review). Other data suggest that catecholamines, such as norepinephrine, are required for stress to induce biomarkers of inflammatory activity in the brain (Blandino et al., 2006, 2009; Johnson et al., 2005; Miller, 2007; Miller et al., 2009). We suggest the additional possibility that the stress-induced microdamage in the brain described in Section 3 above may be a stimulus that contributes to activation of the neuroinflammatory system.

5. Inflammatory mediators can induce depressive symptoms

A body of evidence shows that inflammatory mediators, such as cytokines, are potent modulators of behavior and affect. For example, people who are treated with the inflammatory mediators interferon-α or IL-2 in the course of therapy for various medical conditions unrelated to mood develop Major Depression during treatment at a frequency of 23–45% (Hauser et al., 2002; Horikawa et al., 2003; Musselman et al., 2001; Robaeys et al., 2007) (Lotrich, 2009) (for review). Of those with preexisting depression before cytokine treatment began, most exhibited a worsening of depressive symptomatology (Beratis et al., 2005). Depressive symptoms in cytokine-treated patients respond to antidepressant medication (Musselman et al., 2001), suggesting biological similarity of cytokine-induced depression to depression in general. Even in healthy human volunteers, experimental exposure to an inflammatory stimulus, such as vaccination, elicits depressed mood (Eisenberger et al., 2009; Eisenberger et al., 2010; Harrison et al., 2009; Strike et al., 2004; Wright et al., 2005). In experimental animals, injection of cytokines or lipopolysacharide (LPS, a bacterial endotoxic cell wall component which induces cytokine release) generally leads to depressive behavior in the forced swim and tail suspension tests (Dunn and Swiergiel, 2005; Frenois et al., 2007; Godbout et al., 2008), but see (Deak et al., 2005a,b).

The capacity of inflammatory mediators to induce depression is further supported by the study of individual depressive symptoms. For example, inflammatory mediators induce anhedonia in rodents as measured by decreased sucrose consumption or preference (De La Garza, 2005) (for review). However, sucrose related measures can be confounded with anorexia, a symptom that is also induced by inflammatory mediators. Therefore, intracranial self-stimulation reward has been used as an alternative measure of reward function. Using this procedure, several studies have verified that injection of cytokines or LPS generally results in decreased reward reactivity (Anisman et al., 1996; Anisman et al., 1998; Barr et al., 2003; Borowski et al., 1998; Miguelez et al., 2004), but see (Kentner et al., 2007).

Sleep and appetite disturbances and fatigue, which characterize depression (American Psychiatric Association, 2000), are part of a cytokine-triggered syndrome termed "sickness behavior" that also occurs when an organism has an infection (Dantzer et al., 2008; Konsman et al., 2002) (for reviews). It is now thought that the brain recognizes cytokines as molecular broadcasts of injury or infection, reorganizes the individual's behavior in ways that promote recu-

peration, and that sickness behavior reflects this reprioritization (Dantzer et al., 2008; Konsman et al., 2002). Specifically, cytokines have been found to mediate the changes in sleep produced by infection (Imeri and Opp, 2009) (for review). Evidence also supports a role for cytokines in mediating the appetite changes in depression (Andreasson et al., 2007) (for review).

Difficulty in concentrating or thinking clearly is a symptom of depression (American Psychiatric Association, 2000) that may also be a consequence of inflammatory activation. Acute cognitive impairments have been noted in many situations in which the inflammatory system is activated (Dantzer et al., 2008) (for review), such as after cytokine injection (Rachal Pugh et al., 2001) (for review), peripheral infection, e.g. (Sparkman et al., 2006), tissue injury, such as major surgery (Wan et al., 2007), and chronic inflammatory conditions (Dimopoulos et al., 2006). More specifically, inflammatory molecules affect synaptic plasticity (Boulanger, 2009) (for review).

Somatic complaints, including diarrhea (Sugahara et al., 2004), nausea (Haug et al., 2002), aches (Lecrubier, 2006), and fever (Sugahara et al., 2004), are often associated with depression. These symptoms are also commonly experienced in flu-like illness and are all thought to be induced by inflammatory mediators (Eccles, 2005; Elmquist et al., 1997; Musch et al., 2002).

What is the route by which inflammatory mediators influence behavior? In the case of sickness, the symptoms are triggered by cytokines originating *in the periphery*. Several pathways have been discovered that transmit the inflammatory signal from the periphery to the brain, but engagement of these immune-to-brain communication pathways ultimately leads to the production of proinflammatory cytokines by microglial cells of the brain (Dantzer et al., 2008) (for review). In the case of stress-induced depression, a more parsimonious mechanism for cytokine-induced behavioral change is possible. The inflammatory mediators could *originate* from microglia within the brain.

To recap this section, inflammatory mediators administered to experimental animals induce depressive symptoms, including anhedonia, sleep, appetite and activity level disturbances, cognitive deficits, and other flu-like complaints. Furthermore, in humans, administration of inflammatory mediators can trigger the entire Major Depressive syndrome. These data have led recent reviews to concur that inflammatory mediators can play a role in the generation of depressive symptoms (Dantzer et al., 2008; Miller et al., 2009; Raison et al., 2006).

6. Anti-inflammatory manipulations may have antidepressant effects

Evidence suggests that various anti-inflammatory manipulations have antidepressant effects in experimental animals and in humans. For example, genetic knockout of IL-6 in mice reduces depressive-like behavior in the forced swim, tail suspension, learned helplessness, and sucrose preference tests (Chourbaji et al., 2006). Knockout of the IL-1 receptor blocked stress-induced depressive-like behavior in the sucrose preference and social exploration tests (Goshen et al., 2008). IL-1 receptor antagonist delivered to the rodent brain blocks stress-induced depressive behaviors such as escape deficits (Maier and Watkins, 1995), anhedonia (Goshen et al., 2008; Koo and Duman, 2008), and reduction of social behavior (Arakawa et al., 2009; Goshen et al., 2008).

There is some evidence for an effect of nonsteroidal anti-inflammatory drugs (NSAIDs) on mood (Brunello et al., 2006; Ketterer et al., 1996; Onder et al., 2004). Positive effects of NSAIDs on mood have been noted in humans during therapy for psoriasis (Krishnan R. et al., 2007; Tyring et al., 2006). A small study using the anti-inflammatory agent acetylsalicylic acid found a shortened onset of action of antidepressants as well as an augmentation of their therapeutic effects in humans (Mendlewicz et al., 2006) and in an animal model of depression (Brunello et al., 2006). Likewise, adjunctive treatment with the anti-inflammatory cyclooxygenase-2 inhibitor celecoxib showed superiority over antidepressant alone in the treatment of major depression (Akhondzadeh et al., 2009) and may produce a rapid-onset antidepressant effect in bipolar patients (Nery et al., 2008). Muller and colleagues found that celecoxib has therapeutic effects in major depression in a double-blind, randomized, placebo-controlled add-on pilot study to reboxetine, a selective norepinephrine reuptake inhibitor (Muller et al., 2006). An antidepressant effect of celecoxib has also been reported in an animal model of depression (Guo et al., 2009). Several anti-inflammatory manipulations, including injection of the NSAID indomethacin, relieved depressive-like symptoms in the rodent maternal separation model (Hennessy et al., 2009a) (for review).

Minocycline, which has powerful anti-neuroinflammatory properties (Tikka et al., 2001; Yrjanheikki et al., 1998; Yrjanheikki et al., 1999), is reported to have an antidepressant effect in a human case (Levine et al., 1996) and in animal models of antidepressant activity (Molina-Hernandez et al., 2008a; Molina-Hernandez et al., 2008b; Pae et al., 2008), but see (Deak et al., 2005a,b). Furthermore, positive effects of the anti-cytokine antibody, infliximab on mood in humans have been noted during treatment of Crohn's disease (Lichtenstein et al., 2002).

Systemically administered *steroidal* anti-inflammatory drugs, such as prednisone, have also been noted to affect mood. For example, in one series of human cases, prednisone augmentation of antidepressant therapy showed promise in treatment-resistant depression (Bouwer et al., 2000). Patients taking prednisone for various health concerns are counseled that they may have to endure "inappropriate happiness" as a side effect (U.S. National Library of Medicine and the National Institutes of Health, 2009). While it appears that *short-term* treatment with high-dose prednisone often leads to mania and hypomania, *long-term* treatment leads more often to depression (Bolanos et al., 2004; Brown et al., 2002) (Brown and Suppes, 1998; Brown and Chandler, 2001) (for reviews). In accord with potential opposing effects of acute versus chronic glucocorticoids on mood, together with evidence of chronic hypercortisolemia in some depressed people (Gillespie and Nemeroff, 2005), both administration of steroidal drugs (Bouwer et al., 2000) as well as *blockade* of endogenous cortisol secretion (Gallagher et al., 2008) are being pursued as potential antidepressant therapies.

In addition to these examples of anti-inflammatory treatments that may have antidepressant effects, there is evidence that the antidepressant treatment vagal nerve stimulation (VNS) may have anti-neuroinflammatory activity. Despite some controversy, VNS has received United States Food and Drug Administration (FDA) approval for the treatment of refractory depression and a recent review continues to supports its usefulness (Rush and Siefert, 2009) (for review). The mechanism of action of VNS is open to speculation. Several hypotheses have been ventured, such as that its effectiveness is due to the anticonvulsant effects of VNS or due to neural connections between the vagus and brain regions that regulate serotonin and norepinephrine (Groves and Brown, 2005; Nemeroff et al., 2006) (for reviews). An alternative possibility is that VNS effectiveness in depression is attributable to its effects on the inflammatory system (Corcoran et al., 2005; Das, 2007). VNS is effective against a wide variety of conditions with inflammatory features, such as endotoxemia (Borovikova et al., 2000), experimental sepsis, ischemia/reperfusion injury, hemorrhagic shock, arthritis, and other inflammatory syndromes (Tracey, 2007) (for review). In addition to these effects in the periphery, VNS inhibits neuronal damage after cerebral ischemia (Masada

et al., 1996) and reduces infarct size (Ay et al., 2009). Following traumatic brain injury, VNS protects gamma aminobutyric acid (GABA) neurons (Neese et al., 2007), enhances motor and cognitive recovery (Smith et al., 2005; Smith et al., 2006), and attenuates cortical edema (Clough et al., 2007). These data suggest that VNS may have anti-inflammatory and neuroprotective effects in the brain.

Thus, evidence indicates that anti-inflammatory manipulations have antidepressant actions in humans and animals. Therefore, in addition to inflammatory mediators being *sufficient* to induce depressive symptoms as reviewed in Section 5 above, the evidence reviewed in this section suggests that inflammatory mediators are sometimes *necessary* for depressive symptoms.

7. A therapeutic mechanism of action for antidepressant treatments may involve neuronal plasticity, neurogenesis, and neurotrophins

The degree of efficacy of antidepressant medications in the treatment of depression has been a matter of debate. Two recent meta-analyses (Fournier et al., 2010; Kirsch et al., 2008) that circumvent problems of publication bias (Turner et al., 2008) concur that while the magnitude of benefit of antidepressant medication compared with placebo may be minimal or nonexistent, on average, in patients with mild or moderate symptoms, for patients on the upper end of very severe depression, the benefit of medications over placebo is statistically and clinically significant. The possibility remains that an effect of antidepressants on mild to moderate depression was obscured by a substantial and growing placebo effect (Walsh et al., 2002), which may include a high spontaneous resolution rate (Andrews, 2001; Hrobjartsson and Gotzsche, 2001). Nonetheless, the meta-analyses provide some rationale for continuing research into the mechanism of action of current antidepressant medications.

Antidepressant treatments influence plasticity at the electrophysiological and structural levels. Chronic administration of the selective serotonin reuptake inhibitor and antidepressant fluoxetine restores ocular dominance plasticity in the adult visual cortex as assessed electrophysiologically and behaviorally (Maya Vetencourt et al., 2008). Furthermore, fluoxetine protected hippocampus synaptic plasticity during conditioned fear stress (Spennato et al., 2008). In addition, fluoxetine and the tricyclic antidepressant imipramine induce structural changes in the hippocampus (Bessa et al., 2009; Chen et al., 2008a; Hajszan et al., 2005), the somatosensory cortex (Guirado et al., 2009), and the prefrontal cortex (PFC) (Bessa et al., 2009).

Increases in neurogenesis result from treatment with all major classes of antidepressant drugs, e.g. (Pechnick et al., 2008; Wang et al., 2008; Yanpallewar et al., 2010; Zhao et al., 2008) (for review), as well as with other antidepressant interventions, such as exercise, e.g. (Stranahan et al., 2006; van Praag et al., 2005) and electroconvulsive therapy, e.g. (Perera et al., 2007; Segi-Nishida et al., 2008). Antidepressant treatment-induced neurogenesis has been reported in humans (Boldrini et al., 2009), non-human primates (Perera et al., 2007), tree shrews (Czeh et al., 2001), and rodents (Zhao et al., 2008) (for review), albeit not in all strains. One survey found that fluoxetine increases hippocampal cell proliferation only in those mouse strains that also show a positive behavioral response to treatment (Miller et al., 2008). In one strain of rat, however, the tricyclic antidepressant nortriptyline induced an antidepressant behavioral change in the forced swim test while no increase in neurogenesis was detected (Petersen et al., 2009). In that strain (the genetic depression model, Flinders Sensitive Line) neurogenesis was already elevated compared to the Flinders Resistant Line. Thus in general, but not without exception, antidepressant-induced behavioral change is accompanied by increased neurogenesis.

Importantly, evidence indicates that in some instances, the behavioral effects of antidepressant drugs *depend* on neurogenesis (Zhao et al., 2008) (for review). Antidepressants fail to elicit behavioral effects when neurogenesis is blocked by localized x-irradiation (Airan et al., 2007; David et al., 2009; Santarelli et al., 2003; Surget et al., 2008; Wang et al., 2008), by genetic manipulation of receptor tyrosine kinase trkB on neural progenitor cells (Li et al., 2008), or by pharmacological inhibition of vascular endothelial growth factor (VEGF) receptor Flk-1 (Warner-Schmidt and Duman, 2007). The dependence of antidepressant-induced behavioral change on neurogenesis has been found in various strains of mice (David et al., 2009; Li et al., 2008; Santarelli et al., 2003; Surget et al., 2008; Wang et al., 2008) and rats (Airan et al., 2007; Warner-Schmidt and Duman, 2007). Neurogenesis-dependence has been demonstrated for fluoxetine (Airan et al., 2007; David et al., 2009; Li et al., 2008; Santarelli et al., 2003; Surget et al., 2008; Wang et al., 2008), imipramine (Li et al., 2008; Santarelli et al., 2003; Surget et al., 2008), and the tricyclic antidepressant desipramine (Warner-Schmidt and Duman, 2007). This neurogenesis-dependence has been seen for antidepressant effects on a variety of behavioral endpoints, such as grooming (Surget et al., 2008), anhedonia (Warner-Schmidt and Duman, 2007), immobility in the forced swim test (Airan et al., 2007; Warner-Schmidt and Duman, 2007) and tail suspension test (Li et al., 2008), novelty-suppressed feeding (David et al., 2009; Li et al., 2008; Santarelli et al., 2003; Surget et al., 2008; Wang et al., 2008; Warner-Schmidt and Duman, 2007), and learned helplessness (Warner-Schmidt and Duman, 2007). It should be noted, however, that a minority of studies did not find any neurogenesis-dependence to antidepressant effects on behavior (Bessa et al., 2009; Holick et al., 2008), and the dependence appears to vary in a behavioral endpoint-specific (David et al., 2009) and antidepressant-specific (Surget et al., 2008) manner.

A similar set of findings has been obtained for BDNF. Chronic exposure to a variety of antidepressant treatments increases BDNF expression in various brain regions, e.g. (Conti et al., 2002; Maya Vetencourt et al., 2008; Nibuya et al., 1995; Tsankova et al., 2006; Yanpallewar et al., 2010) and even in the blood circulation of antidepressant-treated human subjects (Brunoni et al., 2008; Sen et al., 2008) (for meta-analyses). Infusions of BDNF into the midbrain (Siuciak et al., 1997), hippocampus (Shirayama et al., 2002; Sirianni et al., 2010), and ventricle (Hoshaw et al., 2005) elicit antidepressant effects in the forced swim test and learned helpless procedure, although opposite effects have been reported for infusion of BDNF into the ventral tegmental area (Eisch et al., 2003).

Studies have shown that the effects of antidepressant drugs on behavior depend on BDNF or its receptor (Chen Z.Y. et al., 2006; Ibarguen-Vargas et al., 2009; Rantamaki et al., 2007; Saarelainen et al., 2003) and have localized this dependence to the forebrain (Monteggia et al., 2004; Monteggia et al., 2007), to the dentate gyrus within the forebrain (Adachi et al., 2008), and to neural progenitor cells within the dentate gyrus (Li et al., 2008). This set of findings intersects with the data showing neurogenesis-dependence of antidepressant drug effects on behavior, as well as with data showing that BDNF generally increases neurogenesis (Henry et al., 2007; Lee et al., 2002; Mohapel et al., 2005; Pencea et al., 2001; Rasika et al., 1999; Rossi et al., 2006; Schabitz et al., 2007; Scharfman et al., 2005) but see (Galvao et al., 2008; Larsson et al., 2002).

In addition to these effects on plasticity, neurogenesis, and BDNF, antidepressants exert anti-inflammatory (Abdel-Salam et al., 2003; Abdel-Salam et al., 2004; Brustolim et al., 2006; Diamond et al., 2006; Kubera et al., 2001; Maes et al., 1999; Roumestan et al., 2007) and anti-neuroinflammatory effects (Hashioka et al., 2007;

Hwang et al., 2008; Lim et al., 2009; O'Sullivan et al., 2009; Tai et al., 2006; Vollmar et al., 2008) and provide neuroprotection (Jin et al., 2009; Lim et al., 2009; Peng et al., 2008) (Lauterbach et al., 2010; Mostert et al., 2008) (for reviews).

Overall, recent literature reviews concur that increases in neurotrophins and neurogenesis are required for at least some behavioral effects of some antidepressants in some strains (Eisch et al., 2008; Krishnan and Nestler, 2008; Martinowich et al., 2007; Sahay and Hen, 2007; Zhao et al., 2008) (for reviews). In addition to the trophic effects, antidepressants appear to have anti-neuroinflammatory and neuroprotective effects.

8. Several theoretical models for the *pathophysiology* of depression have been built with these findings

The above sections review an evidence base of moderate strength for each of the following six conclusions. In humans, depression is often triggered by a stressful life event. Stress induces microdamage and remodeling in the brain. Stress induces signs of neuroinflammatory activation. Inflammatory mediators can trigger many depressive symptoms. Anti-inflammatory treatments may have antidepressant effects. Finally, antidepressants affect neuronal plasticity and, under some circumstances, the effects of antidepressants on behavior are dependent on neurogenesis and neurotrophins. Several authors have used the above findings to develop theoretical models for the pathophysiology of depression.

In the "neurogenesis hypothesis of depression", (i) the decrease in neurogenesis seen with stress, (ii) coupled with the loss of hippocampal volume seen in depressed patients and (iii) the involvement of neurogenesis in the effects of antidepressant drugs on behavior supported the following hypothesis: stress-induced reductions in neurogenesis might be an important causal factor in precipitating depressive episodes (Jacobs et al., 2000; Jacobs, 2002). However, in subsequent studies, there was no indication that blockade of neurogenesis by brain irradiation leads to a depressive phenotype, at least in the forced swim test (Airan et al., 2007; Holick et al., 2008). Likewise, eliminating neurogenesis did not increase sensitivity to the depressive effect of unpredictable chronic mild stress measured on several behavioral tests (Surget et al., 2008). In addition, there are a number of indirect arguments against the possibility that impaired neurogenesis could cause depressive phenotypes (Decarolis and Eisch, 2010; Sahay and Hen, 2007; Sapolsky, 2004) (for reviews). Taken together, recent reviews agree that although the findings are firm that stress leads to decreased neurogenesis and that behavioral effects of antidepressants often require neurogenesis, decreased neurogenesis is not likely to be a causal factor in precipitating depression (Krishnan and Nestler, 2008; Sahay and Hen, 2007).

The BDNF saga is similar to that of neurogenesis. The original version of the "neurotrophin hypothesis of depression" proposed that decreased expression of BDNF contributes to depression (Duman and Monteggia, 2006). However, in general, little effect of genetically reduced BDNF signaling was seen on tests reflecting depressive-like behavior (Adachi et al., 2008; Chourbaji et al., 2004; Li et al., 2008; MacQueen et al., 2001; Monteggia et al., 2004; Saarelainen et al., 2003; Zorner et al., 2003) but see (Monteggia et al., 2007). Data on whether reductions in BDNF increase *sensitivity* to stress-induced depressive behavior are mixed, e.g. (Advani et al., 2009; Ibarguen-Vargas et al., 2009). Overall, recent reviews concur that data do not support the hypothesis that reduced BDNF signaling can cause depressive-like behavior, despite firm findings that BDNF is regulated by stress and that BDNF is required for antidepressant effects (Krishnan and Nestler, 2008; Martinowich et al., 2007).

The "cellular plasticity hypothesis of depression" (Kempermann and Kronenberg, 2003) incorporates features of both the neurotrophin and neurogenesis hypotheses to overcome the limitations of either hypothesis alone, but it has not explicitly incorporated the data implicating the inflammatory system in depression.

Likewise, other hypotheses contain valuable additional insights but are still incomplete. For example, the "hygiene hypothesis", and more accurately the "old friends hypothesis", argues that an immunoregulatory failure precipitated by the unprecedentedly hygienic environment of developed nations is responsible for the rising incidence of chronic inflammatory disorders (Guarner et al., 2006; Rook, 2007, 2009). Invoking data on the involvement of the inflammatory system in depression, Rook (Rook and Lowry, 2008; Rook, 2009) has extended this hypothesis to explain the rising incidence of depression. This hypothesis persuasively argues that this immunoregulatory failure could increase vulnerability to stress-related depression, but the hypothesis has not yet been further elaborated to incorporate data on the involvement of neurotrophins, neurogenesis and plasticity in depression.

In the "macrophage hypothesis of depression", Leonard (Leonard, 2001) argues that stress-induced hypersecretion of glucocorticoids results in a malfunctioning of macrophages and dysregulated release of cytokines which in turn increases glucocorticoids further and leads to dysregulation of noradrenergic and serotonergic neurotransmission and sickness behavior. According to this hypothesis, antidepressants have anti-inflammatory effects on macrophages which lead to a normalization of glucocorticoid release and downstream effects on central neurotransmission. This is an older hypothesis that does not, as is, incorporate the recent data on neurogenesis, neurotrophin, or stress-induced structural changes.

In an elaboration of the "Mayberg model" by Stone and colleagues (Stone et al., 2008), stressful experiences lead to prolonged hypoactivity in the brain's reward circuitry, which in turn reduces neurotrophic and neurogenic support in these regions, leading to disuse atrophy. Simultaneously, the stressful experience leads to overstimulation of the stress circuitry. Stress-sensitizing and reward-inhibiting actions of cytokines contribute to depression. Antidepressants lead to a normalization of these effects and gradually overcome the atrophy.

In the inflammation and neurodegenerative hypothesis of depression (Maes et al., 2009), an inflammatory process triggered by stress enhances neurodegeneration and reduces neurogenesis.

The diversity of these theoretical models reviewed in this section highlights the fact that the phenomena of stress, microdamage in the brain, cytokines, reduced neurogenesis, neuroinflammation, and neurotrophic factors are reciprocally interconnected in many different ways. Many of these theoretical models are not mutually exclusive and very little data exist to distinguish one from another. In fact, these models could conceivably all represent individual facets of a complex of interconnected pathologies that stress can trigger in the brain.

9. These findings can also be assembled into a theoretical scenario for a healthy response to stressful life events

In all of the theoretical models described in Section 8, it is assumed that depression is a result of some kind of *malfunction*. It may be easier to predict how a response can malfunction, however, after first comprehending the cascade of events that comprise its *proper function*. Therefore, we now use the above findings to address what the *healthy* response to stressful life events might be and use that as a framework to clarify and organize ideas of how dysfunction occurs.

9.1. A healthy response to tissue damage includes wound repair during an episode of recuperative behavior

"The complex of melancholia behaves like an open wound . . ." (Freud, 1917/1957).

To build a theoretical model for a healthy response to a stressful event we will start with the stress-induced microdamage in the brain and ask what a typical response to this damage might be (Fig. 1). Generally, when tissue in the body is damaged, a three-stage wound repair process is triggered. An initial phase of wound healing is the demolition phase, in which devitalized tissue is removed and proinflammatory cytokines are released. With the wound cleared of debris, the release of growth factors from various sources triggers a second, regenerative phase of wound repair in which new tissue is formed (Gurtner et al., 2008) (for review). This process involves stem cells which are resident in virtually all tissue types. These cells provide daughter cells that differentiate and directly participate in the structural repair of the wound, and they also supply secreted factors that downregulate the inflammatory response (Stappenbeck and Miyoshi, 2009; Uccelli et al., 2007) (for reviews). Finally, there is a third refinement phase that can take months to years (Gurtner et al., 2008) (for review).

A similar process takes place after brain injury (Blizzard et al., 2010; Wieloch and Nikolich, 2006) (for review). After stroke, for example, a neuroinflammatory response is triggered involving activation of microglia, the resident inflammatory cells in the brain (Kreutzberg, 1996) (for review). After activation, microglia migrate to the site of injury, release proinflammatory cytokines, and phagocytose cellular debris (Kreutzberg, 1996) (for review). In the region of reversible stroke damage called the penumbra, those neurons that do not die lose dendritic spines (Murphy and Corbett, 2009) (for review), as has also been seen after stress (Chen et al., 2008c; Goldwater et al., 2009; Hajszan et al., 2009; Radley et al., 2006). At some point, microglia begin to release growth factors, such as BDNF (Madinier et al., 2009; Rickhag et al., 2007; Sato et al., 2009) which can increase neurite outgrowth and sprouting in the injured brain (Batchelor et al., 1999, 2000, 2008; Chen et al., 2005; Mamounas et al., 2000). In general, functional recovery from stroke is enhanced by (Muller et al., 2008; Schabitz et al., 2004; Schabitz et al., 2007) and is in fact dependent on (Chen et al., 2005; Ploughman et al., 2009) this BDNF signaling, but see (Nygren et al., 2006). By a few weeks after the stroke, dendritic spine turnover and synaptogenesis are apparent, and new functional connections proliferate (Murphy and Corbett, 2009) (for review). These changes can occur in the peri-infarct, as well as connected areas (Carmichael, 2006) (for review).

Although neuroinflammation transiently *inhibits* neurogenesis (Ekdahl et al., 2003; Monje et al., 2003) (Zhao et al., 2008) (for review), injury eventually *increases* neurogenesis, e.g. (Arvidsson et al., 2002; Ohira et al., 2009; Parent et al., 2002; Yu et al., 2008), presumably in the later regenerative phase of brain injury repair. Although neurogenesis only occurs in a small number of brain sites, in the case of stroke the *neural progenitors are able to migrate great distances* to the site of neuroinflammation, a process that is regulated by chemokines (Belmadani et al., 2006). These newborn neurons have been demonstrated to take up residence at the site of injury and integrate synaptically (Arvidsson et al., 2002; Yamashita et al., 2006; Zhang et al., 2007) (Massouh and Saghatelyan, 2010) (for review). In addition to this cell replacement role in repair of the injury, neural stem cells also protect the CNS from inflammatory damage in other ways (Martino and Pluchino, 2006) (for review), including immunomodulation (Pluchino et al., 2005, 2009). These effects presumably help resolve the neuroinflammatory phase and

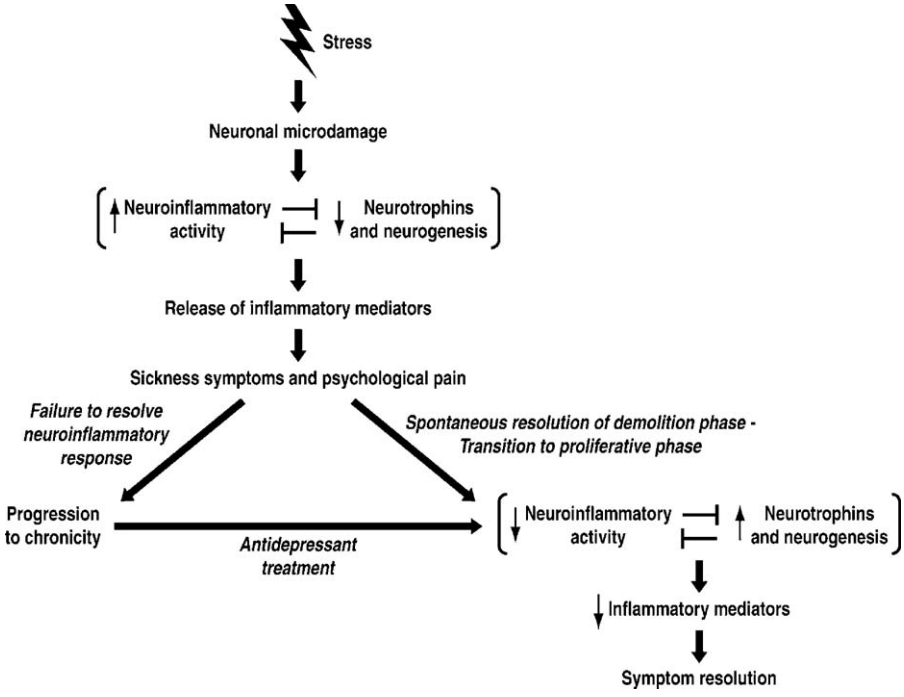

Fig. 1. Theoretical model for depression. In this model, a major adverse stressful life event (reviewed in Section 2) leads to neuronal microdamage, such as a reduction of dendritic length, spines, and branching in the hippocampus and prefrontal cortex (Section 3). Such microdamage elicits a neuroinflammatory response (Section 4) that inhibits neurogenesis and neurotrophin activity (Section 3). The activated neuroinflammatory system releases inflammatory mediators which elicit sickness symptoms (Section 5). In addition, these neuroinflammatory mediators hypersensitize psychological pain circuits by a similar mechanism to that by which they are known to hypersensitize physical pain circuits in the context of bodily injury (Section 9.2). If the neuroinflammatory response fails to resolve, then the depressive episode becomes chronic (Section 10). On the other hand, a healthy inflammatory response will spontaneously resolve and transition to the proliferative phase of injury repair (Section 9.1). In this transition, the decreased neuroinflammatory activity releases inhibition of neurotrophin activity and neurogenesis, and these trophic processes increase. As the injury repair nears completion, the release of pro-inflammatory mediators decrease, allowing depressive symptoms to remit. Because antidepressant treatments have anti-neuroinflammatory effects and lead to an increase in neurogenesis and neurotrophin expression (Section 7), these treatments promote resolution of the injury repair response.

promote the growth phase in the course of brain injury repair. Some months after the stroke, refinement of synaptic connections occurs (Murphy and Corbett, 2009). The end result is that, albeit to a limited extent, neurons have been rewired, function has been recovered, and the brain has self-repaired (Murphy and Corbett, 2009).

In general, wound repair responses are graded on a continuum from para-inflammation to full-blown inflammation. The body reacts to cellular stress, malfunction, or microdamage with para-inflammation to help the tissue restore functionality (Medzhitov, 2008) (for review). Mild cases can be handled by tissue-resident macrophages, while more severe damage requires recruitment of leukocytes and plasma proteins from the circulation as occurs in full-blown inflammation. The degree of activation will determine whether the inflammatory response is detectable using common biomarkers (Medzhitov, 2008).

Another component of the healthy response to injury is behavioral change that supports recuperation. For example, an injured primate might reduce foraging, rest in a safe place and tend its wounds (Dittus and Ratnayeke, 1989). As discussed in Section 5, a similar behavioral syndrome is triggered by cytokines during infection and is typically called "sickness behavior" (Dantzer and Kelley, 2007) (for review) but could equally well be termed "convalescent behavior".

Taken together, the healthy response to brain injury likely involves many of the phenomena that have emerged as important in depression, stress, and antidepressant response. These phenomena include neuroinflammatory activation, cytokines, sickness behavior, BDNF, neurogenesis, and plasticity. Therefore, a theoretical model for the healthy response to stress-induced mild brain injury is as follows: An initial neuroinflammatory phase of brain injury repair inhibits growth while clearing the lesion of cellular debris. During this initial phase, released proinflammatory cytokines induce a motivational reprioritization, sickness behavior, that promotes convalescence. As the repair process transitions to the regenerative phase, trophic influences and neurogenesis gain dominance and inhibit proinflammatory processes. Sickness symptoms ultimately resolve and a final refinement phase of the repair response is carried out (Fig. 1).

9.2. Response to tissue damage includes inflammatory pain and central sensitization of pain pathways: candidate mechanisms for psychological pain during acute depressive episodes

> *". . .the gray drizzle of horror induced by depression takes on the quality of physical pain."* (Styron, 1990).

Postulating an injury repair process for stress-induced microdamage suggests possible molecular mechanisms for the psychological pain in depression. Inflammatory pain is produced during the wound repair process by a large number of mediators in the "inflammatory soup" which act through their respective receptors and signaling cascades to phosphorylate TRP (transient receptor potential) and voltage-gated sodium channels (Hucho and Levine, 2007). This modification alters the thresholds and kinetics of the channels, thereby increasing the sensitivity of the nociceptive neurons. For example, one of these pathways to hyperalgesia (hypersensitivity to pain) is demonstrated by the familiar analgesic effectiveness of NSAIDs. NSAIDs target cyclooxygenase, the enzyme that synthesizes prostaglandins. Prostaglandin E2 (PGE2) is released from activated macrophages after an injury. PGE2 then interacts with its G-protein-coupled receptor on the surface of pain fibers. The resulting stimulation of cAMP (cyclic adenosine monophosphate) production leads to activation of protein kinase A and phosphorylation of sodium channel $Na_v1.8$, thereby reducing the activation threshold and increasing responsiveness of the nociceptors (Hucho and Levine, 2007). In addition to cyclooxygenase inhibition, selective pharmacological blockade of $Na_v1.8$ sodium channels produces antinociception in animal models of neuropathic and inflammatory pain (Jarvis et al., 2007). This type of inflammatory pain lasts the duration of the wound repair process and resolves upon successful healing.

The above mechanisms describe inflammatory pain as it occurs on peripheral neurons at the site of injury. After such a peripheral injury, a similar process can also occur on neurons within the CNS, further augmenting the hypersensitivity to pain. Peripheral injury stimulates glia in the CNS to release inflammatory mediators, such as tumor necrosis factor (TNF)-α, IL-6, IL-1β, prostaglandin, bradykinin, and monocyte chemoattractant protein-1 which increase the sensitivity of central pain pathways (McMahon and Malcangio, 2009) (for review). Thus, a neuroinflammatory mechanism contributes to the sensitization of these central pathways (Gao et al., 2009; Hains and Waxman, 2006; Harvey et al., 2004; Kawasaki et al., 2008; Kohno et al., 2008; Samad et al., 2001; Watkins et al., 2001). This phenomenon of enhanced sensitivity to pain that is mediated by changes in the central, rather than peripheral, nervous system is called "central sensitization" of pain pathways. Note that "central sensitization" of pain pathways should not be confused with sensitization to the effects of drugs of abuse or of psychiatric medication.

Might these mechanisms of central sensitization to inflammatory pain also apply to the psychological pain of depression? A molecular overlap is supported by the finding that IL-1 signaling is increased in the brain with stress (Barnum et al., 2008; Blandino et al., 2006, 2009; Deak et al., 2005a,b; Goshen et al., 2008; Grippo et al., 2005; Johnson et al., 2005; Kwon et al., 2008; Murray and Lynch, 1998; Nguyen et al., 1998), is necessary in the brain for stress-induced depressive symptoms (Arakawa et al., 2009; Goshen et al., 2008; Koo and Duman, 2008; Maier and Watkins, 1995), and is known under other circumstances to rapidly and directly induce pain hypersensitivity in the periphery (Binshtok et al., 2008) and to participate in central sensitization to pain (Samad et al., 2001) (Kawasaki et al., 2008) (for review).

In further support of the possibility of shared mechanisms between physical and psychological pain, it has been proposed on theoretical grounds that psychological pain serves a related function to physical pain in motivating avoidance of certain types of evolutionary fitness-detracting threat (Thornhill and Thornhill, 1989). Empirical evidence bolsters the theoretical similarity between physical and psychological pain. For example, functional magnetic resonance imaging (fMRI) studies suggests neuroanatomical overlap in the processing of physical pain and psychological pain, such as from social rejection (Eisenberger et al., 2003), envy (Takahashi et al., 2009), dread (Berns et al., 2006), empathy for someone else's pain (Singer et al., 2004), and the placebo-responsive component of physical pain (Wager et al., 2004). Behavioral, cognitive, linguistic, and psychological evidence also suggests that physical and social pain operate via common mechanisms (Eisenberger and Lieberman, 2004; MacDonald and Leary, 2005) (for reviews) (Panksepp, 2003) (for comment).

In concluding this section, we propose that, in the context of stress-induced microdamage in the brain, similar molecular and cellular mechanisms that have been elucidated for central sensitization to inflammatory pain may contribute to psychological pain in depression. Thus, in accord with bodily pain, the terms "psychache" (Lester, 2000), "psychological hyperalgesia", "psychological allodynia" (allodynia is pain triggered by stimuli that are not normally painful), and even aching emotional numbness may apply to different characteristics of psychological pain in depression. In addition to central sensitization of psychological pain pathways in depression, we propose that central sensitization also occurs in

physical pain pathways, giving rise to the physical pain complaints that are common in depression (Lecrubier, 2006).

10. Both pain and inflammation are vulnerable to chronicity: candidate mechanisms for dysfunctional depression

"Productive and unproductive depression (reflects) the success or failure of a vital process" (Gut, 1989).

Chronic inflammation is a common mechanism of disease, with the clinical presentation of the disease varying widely depending on which tissue is involved. For example, chronic inflammatory activity can affect lungs, heart, scalp, skin, gums, joints, arteries, bones, muscle, tendon, intestines, as well as CNS sites, such as the spinal cord, caudate putamen, nigrostriatal dopaminergic pathway, and cortex. Chronic inflammatory activity at these sites has been suggested to contribute, respectively, to asthma, myocarditis, alopecia, psoriasis, gingivitis, arthritis, atherosclerosis, osteoporosis, myositis, tendonitis, inflammatory bowel disease, as well as a Amyotrophic lateral sclerosis, Huntington's, Parkinson's and Alzheimer's disease (Frank-Cannon et al., 2009). Almost any tissue is at risk for becoming chronically inflamed, with inflammation at each site giving rise to a unique symptomatology.

The pathological potential for inflammation is unprecedented as a physiological process (Medzhitov, 2008) (for review). Even in a well controlled inflammatory response, collateral damage to surrounding healthy tissue is an unavoidable consequence (Medzhitov, 2008) (for review). Thus, inflammation is both a cause and consequence of tissue damage. When the work of the acute inflammatory response is accomplished, a successful inflammatory reaction will swiftly resolve, thus limiting collateral damage. Resolution is not merely a passive termination of inflammation, but rather an active, tightly coordinated biochemical process involving pro-resolution mediators, some of which are biosynthesized from omega-3 fatty acids (Serhan et al., 2008) (for review).

Chronic inflammation arises under certain circumstances. Chronic persistence of an infectious, injurious, insoluble, or antigenic agent can drive chronic inflammation. It has also been suggested that genetic or lifestyle-mediated interference with resolution (Lawrence and Gilroy, 2007) or tolerance (Rook, 2009) might contribute to chronic inflammatory disorders.

Just as inflammatory responses are prone to becoming chronic, so too are pain responses. Chronic pain develops in a substantial fraction of people who experience common surgeries (10–50%) (Kehlet et al., 2006) (for review), serious bodily injury (44%) (Jenewein et al., 2009), and even mild traumatic brain injury (75%) (Nampiaparampil, 2008) (for review). In addition, sometimes chronic pain develops without any obvious precipitant (Burton, 2003).

Several mechanisms have been elucidated for the transition from acute to chronic or exaggerated pain. If an injury involves damage to the nervous system, then the response leading to inflammatory central sensitization is much exaggerated and creates pain that can persist well beyond the completion of the wound healing process (Latremoliere and Woolf, 2009) (for review). In addition to this neuropathic central sensitization, an interrelated phenomenon in chronic pain is hyperalgesic priming. In hyperalgesic priming, an acute inflammatory insult can prime nociceptors (pain neurons) to develop an exaggerated hypersensitivity to pain upon future inflammatory insult (Reichling and Levine, 2009) (for review).

We suggest that these mechanisms for chronic inflammation and exaggerated pain may also occur during the depressive response, rendering the response pathological (Fig. 1.). First regarding chronic inflammation, in our theoretical model, the stressful life event is injurious to the brain. If a chronic stressor is unavoidable, unpredictable, or uncontrollable, we argue it would be persistently injurious to the brain, driving chronic neuroinflammation and chronic depression. An alternative route to chronic depression might be via immunoregulatory failure precipitated by the high contemporary level of hygiene as proposed by Rook and Lowry (Rook and Lowry, 2008). In our theoretical model, however, we suggest that the CNS is the site of the chronic inflammation giving rise to chronic depression, whereas the Rook and Lowry hypothesis assumes a diffuse peripheral origin for the chronic inflammation that promotes depression.

Regarding chronic pain mechanisms, since injury to nervous tissue leads to exaggerated central sensitization of physical pain circuits, we argue that the stress-induced injury to nervous tissue has a high risk of leading to neuropathic central sensitization of psychological pain circuits and thus to chronic depression. In addition, although the mechanism of hyperalgesic priming was originally described in peripheral nociceptors, it could, theoretically, apply to central "psychological nociceptors" as well.

In sum, if the *proper* functioning of the response to stress-induced microdamage involves pain mechanisms and inflammatory activity, then we propose that *dysfunction* of this response likely occurs via the common complications of pain and inflammation, such as conversion to exaggerated and chronic states.

11. Implications, predictions and future directions

Because our model proposes molecular similarity between the mechanisms of physical and psychological pain (Sections 9.2 and 10 above), it offers a molecular basis to explain suggestive data that analgesics may be effective in depression. For example, opiates were used routinely to treat depression until the 1950s when tricyclic antidepressants were introduced (Ban, 2001) (for review). Several small recent studies continue to support the role of opiates as effective, durable, and rapid therapeutic agents in the treatment of depression (Tenore, 2008) (for review). Additional evidence that analgesics may have antidepressant actions comes from subanesthetic doses of ketamine which act as an analgesic (Annetta et al., 2005). Robust and rapid antidepressant effects result from a single intravenous dose of ketamine in treatment-resistant major depression (Skolnick et al., 2009) (for review).

Depression is often grouped with a large family of other disorders that includes chronic fatigue syndrome, fibromyalgia, and irritable bowel syndrome. This grouping is based on a number of different criteria, including frequent comorbidity with each other (Whitehead et al., 2002), shared response to antidepressant treatments (Hudson and Pope, 1990), common risk factors such as childhood maltreatment (Tietjen et al., 2009), coaggregation in families (Hudson et al., 2003), evidence of stress intolerance (Van Houdenhove and Luyten, 2009), and the absence of ongoing peripheral organ pathology (Burton, 2003). It is thought that these shared features reflect a common, cryptic biopsychosocial etiology, the nature of which has not yet been firmly established. It has also been suggested that this family of disorders may be united by the phenomenon of hyperalgesic priming (Reichling and Levine, 2009) or central sensitization (Yunus, 2007). Because hyperalgesic priming and central sensitization to physical and psychological pain contribute to depression in our theoretical model, it offers a biological scenario explaining why depression seems to be part of this family of syndromes.

Because our theoretical model proposes that stress-induced microdamage in the brain triggers a cascade of neurobiological events leading to the depressive episode, this might explain data indicating that brain injury induced by means other than stress also precipitates depression at a high rate. For example, a few preliminary studies in experimental animals have noted

that depressive-like behaviors follow traumatic or ischemic brain injury, although the studies are not well controlled for confounds (Kato et al., 2000; Milman et al., 2005; Pandey et al., 2009; Shapira et al., 2007) but see (Jones et al., 2008). In humans, depression is a common sequelae of traumatic brain injury (Bombardier et al., 2010), even when mild (Ryan and Warden, 2003). In fact, the symptom overlap between depression and the common "postconcussion syndrome" is substantial (Bryant, 2008; Hoge et al., 2008). Furthermore, there is evidence that late-life depression can be precipitated by accumulated small silent cerebral infarctions that appear as white matter hyperintensities on MRI scans, a phenomenon termed "vascular depression" (Alexopoulos et al., 1997; Sheline et al., 2010; Thomas et al., 2002) (Santos et al., 2009) (for review). Moreover, a third of survivors of overt stroke develop post-stroke depression (Lenzi et al., 2008) (for review).

Our theoretical model encourages testing of emerging drugs that target brain injury, neuroinflammation, and pain for antidepressant effects. For example, an *acute* depressive episode brought on by an acute stressful life event may respond to treatments that target traumatic or ischemic brain injury, e.g. (Xiong et al., 2009), acute inflammation, inflammatory pain, or acute central sensitization to pain. Our theoretical model argues that chronic depression resulting from exposure to chronic unavoidable, unpredictable, or uncontrollable stressors, such as in the chronic mild stress animal paradigm (Willner, 2005), may respond to agents that are effective in *chronic* neuroinflammation or neurodegenerative disease. Occurrences of depression in which a depressive reaction to a stressor is worsened by a prior psychologically traumatic event, such as after repeated maternal separation of guinea pig pups (Hennessy et al., 2009b), may respond to emerging neuropathic pain treatments (Dray, 2008) and inhibitors of protein kinase C epsilon, which block hyperalgesic priming (Reichling and Levine, 2009). Finally, since our model argues that inflammatory activity *within* the brain often contributes to depressive symptoms, the extent to which anti-inflammatory and pro-resolution treatments pass the blood-brain barrier may influence their antidepressant efficacy. Thus, while this theoretical model proposes a common core cascade in depression involving brain injury, neuroinflammation, and psychological pain, within this core, different therapeutic opportunities exist in different types of depression and are highlighted by different animal paradigms.

11.1. What are the mechanisms by which stress produces neuronal microdamage?

In our theoretical model, it is assumed that acute stress induces neuronal microdamage by some unknown mechanism and that this microdamage *in turn* induces neuroinflammatory activity. This assumption requires experimental confirmation because any observed differences between the healthy and affected individuals may always represent either the *cause* or the *consequence* of the disease. Neuroinflammation may be the brain's attempt to repair the stress-induced microdamage as we have hypothesized, but it is also possible that the observed neuroinflammation may instead be the *cause* the neuronal microdamage in the first.

In resolving this classic conundrum, it may be important to consider data from acute and chronic paradigms separately. It is possible that some unknown mechanism initially induces the microdamage in acute depression, but in cases that progress to *chronic* depression, the initial neuronal microdamage is maintained by a self-perpetuating cycle of inflammation-induced tissue destruction that results when the acute neuroinflammatory response fails to resolve for any reason.

Studies using *chronic* paradigms suggest the involvement of chronic glucocorticoids. Chronic glucocorticoid exposure produces a loss of apical dendritic length and branching in the hippocampus that mimics chronic stress-induced microdamage, e.g. (Conrad et al., 2007). Chronic stress-induced microdamage was prevented by cyanoketone, a steroid synthesis blocker (Magarinos and McEwen, 1995a). Further dissection of the pathway suggests a dependence on serotonin and glutamate, as the microdamage that follows chronic glucocorticoid or chronic stress exposure is reduced by tianeptine, an enhancer of serotonin reuptake (Conrad et al., 1999; Magarinos et al., 1999; McEwen et al., 1997; Watanabe et al., 1992c), and by phenytoin, an inhibitor of excitatory amino acid release and action (Magarinos and McEwen, 1995a; McEwen et al., 1997; Watanabe et al., 1992a). There are also scattered reports of chronic stress-induced microdamage being reduced by a variety of other manipulations, such as by protein kinase C inhibition (Hains et al., 2009), by enhancement of GABAergic tone (Magarinos et al., 1999), by antioxidants (Lee et al., 2006c), by estradiol (McLaughlin et al., 2010), and by disruption of the tissue plasminogen activator gene (Bennur et al., 2007). These studies provide many tools by which a causal chain of events between chronic stress and microdamage can start to be assembled.

On the other hand, with *acute* stress, dendritic microdamage can be produced via a mechanism upstream from gluccocorticoids. A corticotropin-releasing hormone (CRH) receptor 1 blocker inhibits acute stress-induced spine loss (Chen et al., 2008c, 2010b). CRH, which is released with stress not only from the hypothalamus, but also within the hippocampus, induces rapid spine loss and dendritic regression in hippocampal cultures (Chen et al., 2008c, 2010b). Because this effect can be seen in culture, CRH's acute effects cannot be mediated via adrenal glucocorticoids. Further exploring these pathways from acute and chronic stress to neuronal microdamage is an important future direction.

11.2. Is a function of the acute depressive episode to dismantle neural circuitry that has been rendered disadvantageous, such as by a life event, and to grow neural tissue mediating new behavioral strategies?

> *"I speak of 'productive depression' when at the end of a period of being depressed there is evidence . . . that . . . some behavior has been reorganized, some plan revised, so that following the depressed episode we function more effectively . . ."* (Gut, 1989).

> *". . . if her patients did not achieve some sort of restructuring, they became chronically ill. Something had interfered with the resolution of their depressed response, she felt, so that it lost its self-limiting quality and became autonomous and self-perpetuating. Again we can use the analogy of the immune response to explain this. If the immune response . . . does not resolve normally, it may become a problem in its own right–an immune disorder."* (Zuess, 2003)

The data we have reviewed so far would suggest that the brain is extremely vulnerable to stress-induced microdamage. Yet to be so easily injured would seem maladaptive. In the case of an acute depressive episode, might stress-induced microdamage in the brain actually reflect neurite autodestruction that serves some sort of adaptive function? Evidence suggests that the stress-induced *structural* remodeling that has been seen at specific brain sites, such as the hippocampus, prefrontal cortex, and amygdala (reviewed in Section 3 above) may be the structural correlates of long-term *behavioral* adaptations to the stressor. For example, stress-induced structural change in the hippocampus is accompanied by change in hippocampal-dependent behavioral tasks, in general enhancing hippocampal-dependent fear-related memory but impairing hippocampal-dependent memories acquired outside of a fear-conditioning context (Kim and Diamond, 2002) (for review). In another example, stress was found to induce selective impairment of attention set-shifting, with no change in reversal

learning, with corresponding structural changes in the two brain regions thought to mediate these behavioral tasks, the medial prefrontal cortex (mPFC) and orbitofrontal cortex, respectively (Liston et al., 2006). The mPFC is also implicated in extinction of conditioned fear. Stress attenuates this extinction in a manner that corresponds with mPFC dendritic retraction (Izquierdo et al., 2006). In another study (Vyas et al., 2002), two different stress protocols that elicited contrasting behavioral effects in the elevated plus maze were accompanied by contrasting structural changes, such that enhanced anxiety-like behavior was accompanied by sprouting in the amygdala (a key structure in the fear circuit) (Rodrigues et al., 2009) (for review). Increases in anxiety, changes in attention, a learning bias for fear-related memories, and a resistance to their extinction that are observed after threatening laboratory stressors could function, in a natural setting, to promote vigilance and aversive memories that enable the animal to avoid future harm from similar stressors. Thus, a possible function for stress-induced remodeling in the brain is to create long-term behavioral adaptations to the stressor.

Is there any evidence that such long-term behavioral adaptations are created during an episode of depressive symptoms? Some support comes from work on a social defeat paradigm in mice. In response to social defeat stress, half of the exposed animals exhibited a transient depressive-like episode and a persistent change in social avoidance behavior. The other half manifested neither of these changes and could therefore be considered resilient to defeat stress (Krishnan V. et al., 2007). Although the authors of those studies interpret these findings as indicating that the persistent social avoidance behavior reflects maladaptive functioning (Krishnan V. et al., 2007; Lagace et al., 2010), another interpretation is possible. Both the resilient and the depressive/avoidance behavioral trajectories may be evolutionarily adaptive under different circumstances. The persistent social avoidance could be a long-term behavioral adaptation to defeat stress that serves to protect the animal from future aggression. In contrast, the resilient trajectory might be evolutionarily adaptive if the costs of the depressive/avoidance behavioral change outweigh its benefits. These studies were done in an inbred strain suggesting that it was not genetic differences that dictated which of the trajectories were followed. Because the persistent social avoidance behavior developed only in the subset of animals that displayed the transient depressive-like episode (Krishnan V. et al., 2007), our alternative interpretation is consistent with the possibility that the neural underpinnings of long-term behavioral adaptations to the stressor are created *during* an episode of depressive symptoms.

Is a neural injury repair process *required* for the development of long-term behavioral adaptation to the stressor? In this social defeat paradigm, both the resilient and the depressive/avoidant groups showed a transient *decrease* in neurogenesis which resolved by 24 h after cessation of defeat stress (Lagace et al., 2010). While the resilient subset showed no further changes in neurogenesis, the depressive/avoidant subset began to demonstrate subsequent compensatory *increases* in neurogenesis (Lagace et al., 2010). Neurogenesis proved to be important for the development of the long-term behavioral change because if neurogenesis were ablated via irradiation, then the development of the persistent social avoidance behavior was attenuated (Lagace et al., 2010). Similar results were seen for BDNF (Berton et al., 2006; Krishnan V. et al., 2007). The spontaneous increase in neurogenesis and BDNF that were detected only in the subset that were experiencing the depressive-like episode supports our wound healing model of the depressive episode. Furthermore, the *requirement* of neurogenesis and BDNF for the full expression of the persistent social avoidance introduces the possibility that the growth phase of the stress-induced injury repair process may be involved in creating the neuronal underpinnings of long-term behavioral adaptations.

What effect do antidepressant drugs have on the development of long-term behavioral adaptations to the stressor? In this social defeat paradigm, the depressive-like episode resolves spontaneously, without requiring antidepressant medication. However, if the animals *were* chronically treated with the antidepressants imipramine or fluoxetine, then the persistence of the social avoidance behavior was blocked or attenuated (Berton et al., 2006). These findings were interpreted by the authors of those studies as further indication that the persistent social avoidance is a maladaptive component of depressive symptomatology (Lagace et al., 2010). Another possible interpretation, however, is that by hastening the resolution of an acute depressive episode, antidepressants can disrupt a function of the episode, which is a slow and delicate process of developing the neural underpinnings of long-term behavioral adaptations to the stressor.

Another paradigm in which such a "behavioral metamorphosis" hypothesis for depression could be tested is the maternal separation model in guinea pigs. Soon after pups are isolated from their mothers, the pups begin to display depressive-like behavior that is inhibited by anti-inflammatory treatments (Hennessy et al., 2009a). Do the pups develop long-term behavioral adaptations to separation, such as a reduction in attachment behavior, during the course of this depressive-like episode? There is some evidence that pups respond differently to the presence of the mother when tested after two weeks of a similar separation protocol, relative to those pups who had not been separated from their mothers (Hennessy and Morris, 2005). Does inhibition of neuroinflammation, neurogenesis, or BDNF during the depressive-like episode inhibit any subsequent reduction of attachment behavior? Can microglial activation, focal cytokine release, and neural structural changes in the brain be detected in parallel with the behavioral change?

Thus, in addition to our theoretical model whereby a stressful event elicits a brain injury repair process involving neuroinflammatory-assisted demolition and subsequent neurogenesis- and BDNF-facilitated growth, here we propose a testable "behavioral metamorphosis" hypothesis for depression: This injury repair response that occurs during an episode of depressive symptoms ultimately functions to remove circuitry that has been rendered disadvantageous and to create the neuronal underpinnings of long-term adaptive behavioral change. Such a behavioral metamorphosis function for depression may also apply to depressions that are triggered by situations other than stressful life events, such as by commitment to unreachable goals (Nesse, 2000).

11.3. Is the depressogenicity of a stressor related to the extent, type and neuroanatomical location of the remodeling that it elicits?

> *"Now in what consists the work which mourning performs? ... Each single one of the memories and hopes which bound the (reward motivation) to the (lost) object is brought up ... and the detachment of the (reward motivation) from it accomplished. ... loss in melancholia would also result in an inner labour of the same kind... If the object had not this great significance, strengthened by a thousand links, to the ego, the loss of it would be no meet cause for either mourning or melancholia."* (Freud, 1917/1957)

What features of the stressor influence the *severity* of the depressive response? Some data are consistent with the possibility that the *extent* of behavioral remodeling that is triggered by the stressor may influence the depressogenicity of that stressor. In humans, for example, the dependency of the event on the patient's own behavior influences the event's depressogenicity. If the patient was judged to have contributed to the adverse event, then its association with the depressive episode is significantly greater than if the event was judged to have been just "bad luck" (Kendler et al., 1999).

Furthermore, events that remove from a person the possibility of enacting a behavioral role, such as being devalued in the role of spouse, parent, or breadwinner, are strongly linked to depressive episodes (Kendler et al., 2003).

What features of a stressor promote a depressive trajectory as opposed to alternative responses to stressful events, such as post traumatic stress disorder (PTSD), or Somatization Disorder? There is some evidence that events involving physical/sexual abuse are more likely to precede Somatization Disorders than to precede depression, e.g. (Modestin et al., 2005; Spitzer et al., 2008). Events that represent danger are more likely to precede bouts of anxiety disorders than depression, whereas the loss of a relationship and other types of losses are especially depressogenic (Kendler et al., 2003; Hammen, 2005) (for review). The finding that loss is more depressogenic than other types of stressors is consistent with many decades of clinical observation, e.g. (Freud, 1917/1957). Thus, different classes of stressors seem to elicit different predominant symptoms.

Interpreting these data in the context of our theoretical work, we propose three hypotheses. First, we propose that different classes of stressors trigger remodeling of different circuits. For example, an event that represents a loss of a source of reward might trigger demolition along the reward circuit, which includes among other sites the hippocampus and prefrontal/infralimbic cortex (Haber and Knutson, 2010) (for review). An event that represents a new source of *danger* might trigger remodeling along the *fear* circuit, which includes the amygdala (Wilensky et al., 2006).

Second, as our theoretical model proposes focal inflammatory activity at the sites of remodeling with localized release of inflammatory mediators there, we propose that *which circuit* the inflammatory mediators are localized to influences *which symptoms* predominate. Just as local inflammatory mediators can alter the threshold for firing of neurons in pain circuits, we argue that these molecules can alter the threshold for firing of neurons of other circuits. For example, raising the threshold for firing of neurons in the reward circuit may lead to anhedonia. Lowering the threshold for firing of neurons in the fear circuit may lead to anxiety. Inflammatory mediators at other neuroanatomical sites might give rise to predominantly somatic symptoms.

Third, just as the *duration and severity* of pain responses vary with the *extent* of bodily injury being repaired, we propose that the duration and severity of depressive symptoms would relate to the extent of the "injury" resulting from the demolition of neural tissue. Thus, a minor adverse event, such as a disappointment, might trigger only modest neural demolition, such as dismantling neural tissue underlying an erroneous reward prediction, induce only subtle activation of the inflammatory system such as para-inflammation, which might induce only brief and mild depressive symptoms like sadness. On the other hand, the loss of a *major* source of reward might trigger extensive demolition that induces the inflammatory system to grade up the continuum toward a full-blown wound repair response. Under these circumstances, the episode of depressive symptoms would be more severe and longer lasting, perhaps sometimes reaching the DSM criteria for a Major Depressive Episode.

These three hypotheses propose mechanisms by which the depressogenicity of a stressor may be influenced by the extent and neuroanatomical location of the injury that the stressor elicits. This provides a basis for the common sense notion that depression is at the extreme end of a continuum that includes ordinary states such as disappointment, sadness, and distress.

12. Limitations

Although our theoretical model integrates six bodies of data (Sections 2–7), it does not propose how to integrate data showing that the hypothalamic-pituitary-adrenal (HPA) axis, female gender, genetics, and the personality trait of neuroticism play roles in risk for depression. Although our theoretical model proposes explanations for acute stress-induced depressive episodes, chronic depression, late-life vascular depression, post-stroke depression, post-concussion depression, the increased risk of depression after traumatic childhood experiences, and the full range of symptoms severity, our model does not address Seasonal Affective Disorder, Bipolar Disorder, or Premenstrual Dysphoria. Further, this model does not propose an explanation for why the hippocampus and prefrontal cortex are particularly susceptible to stress-induced microdamage. In addition, the model does not propose molecular mechanisms by which serotonin or norepinephrine reuptake inhibitors lead to enhancement of neurogenesis, BDNF, and plasticity and have anti-inflammatory and neuroprotective actions. Nor does it explain the antidepressant efficacy of Cognitive Behavioral Therapy, Electroconvulsive Therapy, or Transcranial Magnetic Stimulation. The model presented here does not propose what specific symptom criteria could be used to distinguish a *well-functioning* acute depressive response from a *malfunctioning* response. Nor does it indicate what cutoff would distinguish *acute* from *chronic* depression.

We do not discuss the large and growing field showing differential fMRI responses in various brain regions of depressed versus nondepressed individuals. One possibility is that these fMRI differences may be the neurobiological correlates of the differences in affective processing that are produced by cytokines and contribute to the motivational reprioritization of sickness behavior (Harrison et al., 2009).

Although the hypothesis elaborated in the present article suggests a molecular mechanism for psychological pain and physical pain in depression, it does not propose a molecular mechanism for other symptoms or common comorbidities of depression, such as anxiety (Shorter and Tyrer, 2003), irritability (Snaith and Taylor, 1985), guilt (American Psychiatric Association, 2000), and worthlessness (American Psychiatric Association, 2000), nor does it provide a mechanism by which inflammatory mediators in the brain induce the sickness symptoms that are common in depression, such as sleep and appetite disturbances (American Psychiatric Association, 2000), fatigue (American Psychiatric Association, 2000), nausea (Haug et al., 2002), diarrhea (Sugahara et al., 2004), and fever (Sugahara et al., 2004). In a separate manuscript (Wager-Smith, in preparation), we present a theoretical model whereby these symptoms respresent a family of behavioral defenses that are controlled by neuronal circuits for which the trigger threshold can be altered by inflammatory mediators.

Two additional symptoms of depression have not been discussed in this review nor in the manuscript just mentioned: recurrent thoughts of death/suicide and psychomotor retardation/agitation (American Psychiatric Association, 2000).

Thus, although we have integrated many bodies of data into our theoretical model for depression, many relevant findings and symptoms of depression remain to be incorporated. Many hypotheses and predictions that emerge from this model will need to be tested before it can be determined whether this model is a solid foundation upon which a more complete understanding of depression can be built.

13. Conclusion

In this article, we have reviewed data supporting a theoretical model for the biological etiology of depression. This model uses a novel scenario for the healthy functioning of the response to stress in order to predict sources of pathology in depression. In this model, what could be considered emotionally traumatic brain injury, eTBI, triggers a neuroinflammatory-facilitated injury repair

response. The sickness symptoms of depression are induced by the released inflammatory mediators which also produce central sensitization of psychological pain circuits. As after stroke, the injury triggers neurogenesis at remote brain sites and produces newborn neurons that migrate to the sites of injury across the brain. The depressive symptoms remit if the healing process is successful, if the neuroinflammatory response resolves rather than becoming chronic, and if the transition to an exaggerated psychological pain state is avoided. This depressive response is graded so that weak stressors would induce only mild and short-lived depressive symptoms like ordinary sadness.

However, pathological outcomes develop frequently, as they do after serious bodily injury, and can lead to chronic psychological pain and lasting disability. If chronic neuroinflammation occurs, then inflammatory-mediated destruction of tissue at some brain sites can lead to loss of material that is detectable macroscopically. Furthermore, hyperalgesic priming can lead to exaggerated reactions to trivial stressors, allowing future depressions to develop without any apparent precipitating event.

According to one hypothesis that emerges from this theoretical model, this stressful life event-triggered injury repair process may serve a greater function, that is to dismantle neural circuitry that has been rendered disadvantageous by the life event, and to generate neural underpinnings of an updated behavioral program. Within this view, if a behavioral or physiological solution to the stressful predicament is not possible, this might provide an additional route to dysfunction of the depressive response.

These various types of exaggerated and malfunctioning depressive responses will likely be overrepresented in the subset of individuals who seek treatment. If individuals with such pathological depression receive antidepressant medications, these treatments have a number of effects that may tip a growth/pruning balance in the brain by inhibiting destruction and promoting growth of neural tissue (Fig. 1). Such a constellation of effects would be expected to accelerate, but not to instantaneously terminate, the healing process. This may explain the several-week-long delay in apparent antidepressant efficacy. On the other hand, if an acute, well-functioning depressive episode is treated with antidepressants, such accelerated healing might disrupt the delicate process of creating the long-term neural and behavioral changes that were necessitated by the stressor.

Our theoretical model for depression suggests answers to many questions such as what is the source of inflammatory mediators that have been detected in the blood circulation of depressed patients (brain injury), how does vagal nerve stimulation exert antidepressant efficacy (through anti-neuroinflammatory effects), how does traumatic and ischemic brain injury lead to depression (the brain injury repair process induces depression), why does depression share features with a family of other chronic disorders (they share a central sensitization or hyperalgesic priming pathophysiology), and how do analgesic and anti-inflammatory drugs exert antidepressant effects (via shared mechanisms for psychological and physical pain). Our theoretical model encourages drug discovery efforts for depression to include testing emerging analgesic, anti-neuroinflammatory, and neuroprotective agents in animal depression paradigms that are chosen to match each of their unique hypothesized etiologies with the process that the drug targets.

The concept, that a healthy function of a depressive episode is to accomplish some sort of enduring psychological transformation, has a long history in an extremely broad variety of disciplines, both scientific and nonscientific. For example, psychoanalytic observations have led to the proposal that depression consists of an inner labor that allows a person to detach from some entity which he/she had become attached to but had subsequently lost (Freud, 1917/1957) and that resolution of depression involves some type of inner restructuring such as behavioral reorganization, revision of plans, or abandoned strivings (Gut, 1989). Animal and human psychological studies led to the proposal that depression is a stage in the incentive-disengagement cycle during which the individual terminates a commitment to pursue a particular incentive (Klinger, 1975). An evolutionary argument posits that the low mood in depression can foster disengagement from unreachable goals (Nesse, 2000). An integration of each of these notions of depression with conceptions drawn from other sources, including Native American spiritual traditions and the philosophy of homeopathic medicine, led to the proposal that depression is a healing response that functions as a mediator of personal transformation (Zuess, 2003). Observations in clinical sociology indicate that depression enables a change in social roles (Fein, 1990). A neuropsychoanalytic argument holds that sadness functions to decouple outdated stimulus-reward associations, thereby correcting reward prediction errors (Freed and Mann, 2007; Freed, 2009). Each of these disparate perspectives also emphasize that depressive responses sometimes fail in their adaptive function, go awry, and create clinical depressive illness. Our theoretical model for depression suggests molecular and cellular processes that may underlie this widely proposed psychological transformation function and its vulnerability to dysfunction.

In our scenario, the depressive episode can be considered analogous to a period of convalescence from a serious injury, such as a broken pelvis. If one were unfortunate enough to have to endure an unmedicated recuperation from this analogous injury, a two or more week long period of clinically significant distress and impaired social and occupational functioning would certainly be expected. It would not be hard to imagine that most of the day, nearly every day, the victim of one of these incidents would experience markedly diminished interest in almost all activities, diminished ability to concentrate, appetite disturbances resulting in significant weight loss or gain, insomnia or hypersomnia, fatigue, as well as pain, anxiety, irritability, and an unwillingness to get out of bed. Despite meeting the DSM criteria for Major Depressive Disorder, a diagnosis of a "disorder" would not be given here because an exclusion criterion is met (American Psychiatric Association, 2000): The symptoms are due to a medical condition—a major injury. Future study will discern whether the DSM inclusion criteria for Major Depressive Disorder can be reached by a well-functioning depressive response to severe stress-induced neuronal *injury* in the absence of any mental *illness*, in addition to being reached by individuals with a malfunctioning depressive response.

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