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Neuroplasticity in cognitive and psychological mechanisms of depression: An integrative model

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Abstract

Chronic stress and depressive-like behaviors in basic neuroscience research have been associated with impairments of neuroplasticity, such as neuronal atrophy and synaptic loss in the medial prefrontal cortex (mPFC) and hippocampus. The current review presents a novel integrative model of neuroplasticity as a multi-domain neurobiological, cognitive, and psychological construct relevant in depression and other related disorders of negative affect (e.g., anxiety). We delineate a working conceptual model in which synaptic plasticity deficits described in animal models are integrated and conceptually linked with human patient findings from cognitive science and clinical psychology. We review relevant reports including neuroimaging findings (e.g., decreased functional connectivity in prefrontal-limbic circuits), cognitive deficits (e.g., executive function and memory impairments), affective information processing patterns (e.g., rigid, negative biases in attention, memory, interpretations, and self-associations), and patient-reported symptoms (perseverative, inflexible thought patterns; inflexible and maladaptive behaviors). Finally, we incorporate discussion of integrative research methods capable of building additional direct empirical support, including using rapid-acting treatments (e.g., ketamine) as a means to test this integrative model by attempting to simultaneously reverse these deficits across levels of analysis.

Introduction

Depression is the leading cause of disability worldwide with a public disease burden of staggering proportions[1]. While efficacious treatments have been available for decades, remission rates are low, relapse rates are high, and disorder prevalence rates remain notably stagnant, with only 12.7% of patients receiving minimally adequate treatment[2]. At the molecular level, depression has been characterized as a failure of neuroplasticity, including neuronal atrophy and synaptic depression in the medial prefrontal cortex (mPFC) and hippocampus[3–5]. At the neurocognitive level, depression has been called a disorder of impaired cognitive flexibility and prefrontal inhibition[6–8], leading to inflexible negative biases in cognition, such as rigidly held negative beliefs[9].

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Impaired neuroplasticity is theorized to underlie depression, but an empirical divide separates molecular models from cognitive/information processing models that motivate gold-standard behavioral treatments for depression. In this integrative review, we propose a model of neuroplasticity as a multi-level construct, conceptually linking relevant empirical findings across molecular/neuronal, neural network, cognitive, implicit information processing, and clinical levels of analysis. We highlight research approaches that help to bridge this divide. As an example, we discuss the potential for ketamine—which exhibits both rapid plasticity-enhancing effects in animal models[4,10] and rapid clinical effects in human patients[11,12]—to provide a test of the predictions of this integrative model, including simultaneous and correlated reversals of multiple plasticity-related deficits across levels of analysis.

Neuroplasticity models of depression

Studies of the molecular and cellular mechanisms underlying depressive-like behaviors in rodent models and convergent brain imaging and postmortem studies of depressed patients have provided significant advances in our understanding of mood disorders. These findings reveal alterations at the levels of intracellular signaling, gene expression, neurotrophic factors, neurogenesis, neuroinflammation, excitatory and inhibitory neurotransmission, and synaptic number and function, and have been described in several brain regions implicated in depression[13–22]. The signaling pathways and types of molecular and cellular events vary depending on the brain regions studied. Studies have focused on PFC, hippocampus, amygdala, the ventral tegmental area-nucleus accumbens (VTA-NAc) dopamine system, and the HPA axis. These findings have resulted in complementary theories of depression and antidepressant response that have been linked, either directly or indirectly, to the molecular and cellular signaling mechanisms that mediate synaptic plasticity, and have therefore contributed to a broader neuroplasticity hypothesis of depression[3–5]. One of the leading theories highlights the roles of the PFC and hippocampus, including disruption of neurotrophic factors and synaptic connectivity that are related to neuroplasticity mechanisms[4,5]. According to this model of depression, chronic stress leads to sustained decreases in neuroprotective factors [e.g., brain-derived neurotrophic factor (BDNF) expression and signaling] that damage or hinder plasticity, fostering neuronal atrophy and decreased synaptic number and function, particularly in the mPFC and hippocampus[3,4]. This results in deficient adaptation to the environment, compromising learning and stress coping, and to downstream gain of activity in some ‘limbic network’ regions regulated by the PFC. One of the key efferent targets of mPFC is the amygdala, a region involved in control of fear and anxiety and widely implicated in human depression[23]; other output regions include the dorsal raphe, which has been linked to helplessness behavioral deficits (e.g., loss of control); the lateral habenula, associated with anhedonic and aversive responses; and the bed nucleus of the stria terminalis, another region linked with anxiety and negative emotion[22]. Conversely, when neuroplasticity is enhanced (e.g., by treatment), synaptic contacts increase, enhancing adaptability by allowing activity-dependent competition to stabilize the neural structures that best represent internal and external conditions[24–26]. These basic neuroscience findings are linked directly to shifts in depression-like behaviors in animal models, such as performance on the forced swim test, a probe of “despair,” the novelty

suppressed feed test, a probe of “anxiety”, and the sucrose preference test, a probe of “anhedonia.”[27]

Molecular and cellular studies have examined the intracellular signaling pathways underlying the regulation of synaptic function by stress and antidepressant treatments. Repeated stress decreases the expression of BDNF in limbic and cortical brain regions, notably the hippocampus and PFC[4,5,22]. In addition, repeated stress exposure decreases mTORC1 signaling, which is required for synapse formation and neuroplasticity[28], and inhibition of mTORC1 decreases synapse formation in the PFC and is sufficient to cause depression-like behaviors in rodents in the absence of stress exposure, demonstrating a causal relationship between synapses and behavior. Recent evidence demonstrates that chronic stress also leads to activation of microglia, the brain’s resident immune cells, which engulf synapses on nearby pyramidal neurons and thereby contribute to neuronal atrophy[29]. It is also notable that in some brain circuits, stress and depression may lead to enhancement of neuroplasticity mechanisms. For example, studies demonstrate that social defeat stress increases BDNF in the VTA-NAc pathway, leading to enhanced function that is thought to contribute to disruption of reward and motivation behaviors in depression[20,21]. There is also evidence that repeated stress causes hypertrophy of pyramidal neurons in the basolateral nucleus of the amygdala that could contribute to altered anxiety and emotion[30,31]. These findings demonstrate the diversity of the disruptions of plasticity in depression that vary according to brain circuitry and the underlying function regulated by different brain regions.

Clinical evidence provides some further support for the relevance of neuroplasticity mechanisms in depressed patients, though not all findings are consistent. Ketamine, a glutamatergic agent used routinely for induction and maintenance of anesthesia, exhibits well-replicated, rapid, potent antidepressant effects in randomized controlled trials (i.e., metaanalytic Cohen’s d=1.4, a large effect)[12], even in difficult-to-treat conditions such as treatment-resistant depression[32] and bipolar depression[33]. In addition, the FDA has recently approved a nasal application of (S)-ketamine, referred to as esketamine (Spravato), for treatment resistant depression. The rapidity and magnitude of ketamine’s effects have been attributed to its ability to rapidly reverse neuroplasticity deficits in animal models[3,4,10,34]. A single dose of ketamine increases BDNF release and stimulates mTORC1 signaling, which leads to increased levels of synaptic proteins (i.e., GluR1, PSD95, and synapsin 1) and increased number and function of synapses in the PFC[4,22,35]. An elegant recent study provided further evidence that new synapse formation is causally related to the antidepressant actions of ketamine[10]. Using in vivo two photon imaging, ketamine reversed the loss of synapses caused by stress, while selective deletion of these new synapses blocked the sustained antidepressant-like behavioral actions of ketamine.

Of note, however, rapastinel, another drug that reverses synaptic plasticity deficits and exhibits antidepressant-like effects in rodent models[36,37], has been studied in 3 clinical trials to date with relatively weak evidence for its efficacy[38]. Given that clinical studies in depression are subject to well-known confounds including strong placebo responsivity and heterogeneous clinical presentations, further trials may be warranted to clarify rapastinel’s antidepressant efficacy. Regarding the specific role of mTORC1, a recent preliminary study[39] found that rapamycin, an agent capable of blocking mTORC1, when given

concurrent to ketamine infusion, did not block ketamine's antidepressant efficacy (as was expected), but rather extended the window of ketamine's antidepressant effect. However, the authors speculated that the dose of rapamycin (6 mg oral) may in fact have been insufficient to block mTORC1 in the brain, and that rapamycin's potent, peripheral anti-inflammatory actions most likely account for the observed paradoxical effect. Both basic and clinical research have vital and complementary roles to play in the ongoing developing, testing, and refining of neuroplasticity theories of depression.

Integrative hypothesis

In spite of these findings suggesting crucial links between neuroplasticity mechanisms and behavioral tests in animal models, a fundamental translational question remains with respect to the alleviation of complex, multifaceted human conditions: how, precisely, might neuroplasticity mechanisms profoundly alter human experience? Our focus in the current review is to specify potential downstream results of molecular plasticity impairment observable at more 'macro' levels of analysis. In humans, depression and chronic negative affect are associated not only with decreases in convergent molecular and cellular neuroplasticity markers (e.g., BDNF[40]; prefrontal synapses measured post-mortem[41]), but also with altered functional integration across PFC and limbic (e.g., hippocampus, amygdala, striatum) circuits[8,42–44]. Such neural network alterations are posited to contribute to impaired regulatory control of stimulus-driven affective processing[7,45], producing rigid negative biases evident across a wide range of implicit information processing domains (e.g., negative appraisals of self, the environment, and the future[46]; preferential attention and memory for negative stimuli[45,47]). These neural and implicit cognitive patterns may in turn contribute to impaired overall cognitive and behavioral flexibility[6,48] and help to maintain and reinforce a state of high negative affect by fostering overestimation of the personal shortcomings, dangers, and misfortunes inherent to the individual's life[9]. Although psychological and neurocognitive accounts of depression have not typically been united with neuroplasticity findings into a single integrative theory, strong parallels are suggested by overlap in the implicated brain regions (e.g., mPFC, hippocampus, amygdala) and behavioral sequelae (rigid responses to the environment). On this basis, we propose an integrative model of neuroplasticity and mood that bridges these levels of analysis (Table 1; Figure 1).

Plasticity impairments in neural networks

Consistent with the predictions of animal models, hippocampal and PFC volumes are robustly decreased in depressed patients, according to *in vivo* structural imaging[5]. Recently compiled large imaging corpuses, which include >1000 unipolar depressed patients and many thousands of healthy control participants, have documented particularly robust decreases in hippocampal volume[49], which were driven by individuals with recurrent depression and early age of onset (≤age 21), suggesting the impact of the depressed state on hippocampal volume may be cumulative across time and/or episodes. Amygdalar volumes were likewise decreased, but only in patients with early-onset depression, and this finding was not statistically robust after correcting for multiple comparisons. In PFC subregions, robust decreases in cortical thickness were observed in medial and orbital areas of the PFC

and anterior cingulate cortex (ACC)[50], which constitute subdivisions of the rodent "mPFC" homologue (Figure 1). Convergent meta-analytic findings suggest disrupted white matter microarchitecture in depressed patients in key white matter tracts that facilitate inter- and intra-hemispheric integration across PFC and limbic regions, including the corpus collosum, front-occipital fasciculus, and PFC projection fibers[51].

Given that brain structure constrains functional networks[52], these volumetric changes are hypothesized to underlie abnormalities observed in functional neuroimaging measures within the same circuits. Brain processes may best be characterized as the coordinated activity of disparate brain regions over time[53]. Functional connectivity measures (i.e., the temporal correlation between spatially remote neurophysiological events) may be a particularly relevant marker of plasticity deficits, as these indices directly quantify the degree to which regions of the brain act in a coherent fashion and/or influence one another over a second-to-second timeframe. Thus, connectivity indices, often measured with neuroimaging methods such as fMRI, may provide a crucial intermediary, helping to bridge structural neuroplasticity markers (e.g., synaptic dysconnectivity) to downstream alterations in the brain's 'output,' i.e., mental and cognitive processes. When using meta-analytic techniques to identify the most robust patterns across individual studies, depression has been associated with decreased 'intrinsic' functional connectivity (i.e., connectivity observed during a resting state) within and between PFC and limbic networks, including decreased connectivity between mPFC and limbic/affective regions including the hippocampus and amygdala[54]. Depression has likewise been linked to decreased 'global' intrinsic connectivity between the medial and lateral PFC and all other regions of the brain[55], and to decreased inter- and intra-hemispheric integration within and across dorsolateral PFC, medial PFC/ACC, hippocampus, and parietal regions[56,57]. Notably, these connectivity decreases are evident in spite of simultaneously *increased* intrinsic connectivity in other, spatially overlapping networks (e.g., within the midline "default mode network"[54,58]), suggesting connectivity aberrations in depression are circuit-specific.

Similarly, during task states requiring processing of affective stimuli (e.g., evaluating the personal relevance of negative/positive attributes; viewing negative pictures), depressed patients have shown decreased functional connectivity between lateral PFC and amygdala[44] and/or hippocampus[59] and across medial PFC/ACC and limbic regions[60,61]. During 'cognitive reappraisal' tasks, in which volitional attempts are made to down-regulate subjective negative responses to negative stimuli[62], depressed patients have shown decreased activation in lateral and medial PFC coupled with increases in amygdalar response[63,64], and altered mPFC-amygdalar connectivity[65], suggesting impaired volitional PFC regulation of the amygdala. Collectively, these patterns observed in human patients are consistent with the premise that neuronal and molecular plasticity deficits may feed forward to impairments in the coordinated function of prefrontal and limbic regions[66], resulting in impaired PFC regulation and unchecked stimulus-driven responses to salient negative stimuli.

Plasticity impairments in cognition

Structural and neural circuit alterations described above may contribute to performance deficits observed in depressed patients during cognitive and neuropsychological tasks. These

deficits are consistent with an impaired capacity to engage flexibly with external stimuli and efficiently exert goal-directed cognition in support of task demands, thereby reducing flexible, adaptive behavior in complex environments[67]. Meta-analysis of executive functions in depressed patients suggest pronounced deficits (Cohen's $d \geq 1.0$) in cognitive flexibility, inhibition capacity, and verbal fluency, as well as moderate impairments in strategic planning and organization[68,69]. Attention and concentration are also broadly impaired[70,71]. These wide-ranging executive deficits suggest a broad impairment in the ability to control and regulate other lower-order functions and behaviors, including the ability to initiate and stop actions, to monitor and change behavior to match shifting demands of the environment, and to plan optimal behaviors in the face of novelty[69]. Such abilities rely on the integrity and coordinated function of both lateral and medial PFC and ACC subregions[72,73], paralleling the neuronal and neural network levels (as described above), and are believed to contribute fundamentally to depressed patients' substantial functional impairments[74]. Correspondingly, computerized cognitive training interventions, designed to rehabilitate core prefrontal cognitive functions (e.g., working memory) through repeated task practice, show preliminary meta-analytic evidence of acute efficacy in the treatment of depression, including moderate effects on symptom severity and daily functioning[75,76].

Memory deficits are also apparent in depressed patients. These include impairments in both prospective memory for new information—across a variety of domains and task conditions[77]—and retrospective autobiographical memory retrieval, wherein a lack of specificity in retrieved memories ("overgeneral memory") has been described[78]. Overgeneral memory is correlated with reduced problem-solving performance[79] and imageability of future events[80], suggesting the lack of specificity in recalling past life events constrains the 'cognitive set' of viable possible actions that are readily available to conscious awareness. Memory deficits in depressed patients have long been hypothesized to relate directly to neuroplasticity deficits within the hippocampus[81], given its key role in memory formation and retrieval. However, circuit-level dysfunctions impacting connectivity within and across multiple PFC and limbic regions may best explain the breadth of cognitive impairments observed in depression, collectively reducing the individual's capacity to flexibly adjust in response to a continually changing environment.

Plasticity impairments in affective information processing patterns

In addition to cognitive deficits on neuropsychological tests (utilizing standardized, ostensibly neutral stimuli), depression is characterized by rigid, valence-specific biases in the processing of affective information. These biases create preferential processing of negative information (i.e., up-regulation of the 'negative valence system'), and decreased engagement with positive information (down-regulation of the 'positive valence system'), across a range of information processing domains, including attention, memory, interpretation, implicit associations (e.g., negative representations of one's self), and learning and decision-making[8,82].

Attention, which acts as an initial filter on the information entering conscious awareness, shows valence-specific alterations in depressed patients including attentional preference for dysphoric stimuli and biases away from positive stimuli[45,47,83]. In addition, depressed

patients show impaired inhibition of negative information[7]. As these factors result in a greater share of negative (relative to neutral and positive) information being passed forward for further processing, they likely contribute to additional biases documented at later, more 'elaborative' stages of cognition, including preferential recall of negative over positive information[84,85], and biases towards negative interpretations of ambiguous words and word fragments, images (e.g., facial expressions), and scenarios[86–88]. Finally, depression has been associated with stronger implicit associations between the mental concept of oneself and negative characteristics, e.g., lower implicit self-esteem, as measured by performance-based indices[89–91]. Stronger implicit associations between self and suicide-related constructs (e.g., death)[92], as well as stronger attentional bias towards suicide-related words[93], have further been linked to prospective risk of suicide attempts, suggesting a link between affective processing biases and the most severe consequences of depression.

Within the positive valence system, depression involves prominent alterations in the processing of reward cues, such as decreased hedonic pleasure or 'liking' of positive stimuli, decreased reward anticipation, and altered reinforcement learning, which are believed to culminate in decreased motivation to act[94]. Recently, computational approaches have been applied in an effort to further dissect these biases and unveil their component neurocomputational processes. Findings from this emerging literature suggest several impairments in reinforcement learning, or the process of maximizing reward and minimizing loss by modifying behavior in response to experience, which plays a central role in decision-making[95]. For instance, depressed patients exhibit both hyposensitivity to rewards and oversensitivity to punishments[96,97], attributed to alterations in mesolimbic prediction error signaling[97–99], and may exhibit a constrained option space ("tunnel vision") during decision-making[100]. Broadly, positive valence system deficits are linked primarily to altered dopaminergic and/or opioid signaling within midbrain striatal circuits[94,101], but may intersect with plasticity impairments and dysconnectivity of excitatory glutamatergic synapses in an overlapping prefrontal-mesolimbic circuit[5] to produce the full spectrum of affective biases seen in depression.

Though the etiology of these affective information processing biases is not fully understood, the neuroplasticity model of depression suggests a two-fold process: 1) chronic stress, adversity, and negative life events (e.g., parental and/or social interactions) promote learning of negative associations and expectations via normative, experience-dependent plasticity mechanisms, which include evolutionarily preserved mechanisms that prioritize the learning and retention of negative and emotionally salient information[102,103]; 2) such learning is further entrenched through simultaneous, stress-induced decreases in overall plasticity within the prefrontal-limbic circuit, resulting in inflexible, intractable biases that are resistant to subsequent environmental inputs (e.g., positive/disconfirming information). Consistent with our integrative framework (Table 2), the neural substrates of affective biases have been posited to involve inadequate PFC regulation of stimulus-driven limbic responses[8,47] and generalized deficiencies of cognitive inhibition[7]. Negative biases in attention[42,43,104,105] and self-representations[44] have been directly linked to reduced functional connectivity in prefrontal-limbic circuitry, suggesting these neural and behavioral features of depression could reflect a unitary plasticity impairment, expressed across levels of analysis. Biased patterns of information processing might then constitute a final pathway

to negative affect and self-reported symptomatology (discussed further below), via their chronic and cumulative influence on the individual's day-to-day perceptions and experiences[82,106–109]. Further integrative research is needed to evaluate this multi-domain hypothesis.

Plasticity impairments in self-reported psychological symptoms

Though depression is a highly heterogeneous and complex syndrome, it is notable that the clinical phenomenology of depression includes multiple prominent markers of inflexible thought and behavior, which are broadly consistent with a decreased capacity for the brain to flexibly adjust and reorganize itself in response to a changing environment[6]. The two hallmark mood symptoms of depression—at least one of which is required to diagnose a major depressive episode[110]—are persistent dysphoric mood and persistent anhedonia (the inability to experience pleasure), mirroring the two major forms of information processing bias (positive and negative valence systems) discussed above. Rumination, a form of perseverative negative thought pattern, is a prominent risk factor for depression[111]. Similar perseverative thought patterns, such as worry, ruminative post-event processing, and obsessional thinking, are transdiagnostic features of other (often comorbid) negative affective conditions, leading to the hypothesis that repetitive negative thinking is a core, cross-cutting feature of disorders of negative affect[112]. Depressive "schemas," the principle treatment target in gold-standard cognitive-behavioral interventions[113], are likewise characterized by rigid, over-generalized negativity with regard to perceptions of self, future, and the world[9]. Efficacious cognitive-behavioral treatments therefore focus on the goal of expanding plasticity within the perceptions and conscious representations of the patient's internal and external worlds, through repeated, deliberate practice in recognizing and correcting maladaptive, excessively negative thought patterns[114]. Mindfulness-based cognitive therapy, which can effectively forestall the return of depression among individuals with a depression history[115,116], has similarly been characterized as an effort to increase mental flexibility in response to the environment, specifically through the practice of "de-centering," or learning to perceive one's thoughts, feelings and reactions from an objective, non-judgmental, and accepting stance[117].

The behavioral repertoire reported by depressed patients likewise lacks flexibility and diversity, characterized by symptoms of social withdrawal, behavioral deactivation, lassitude, 'vegetative symptoms' (e.g., loss of appetite and libido), and amotivation[110,118,119]. Depressed patients report that a constrained set of possible actions appear viable, paralyzing action and decision-making[120]. Behavioral activation, a psychotherapy that aims to directly increase activity, can effectively treat depression through a concerted effort to expand on points of contact between the patient and their environment, thereby stimulating natural opportunities for positive reinforcement to be received[119,121,122]. Thus, plasticity and diversification within the realm of volitional actions may likewise be antithetical to the state of depression.

Testing predictions of the integrative model: Intravenous ketamine as a test case

Our integrative model predicts the falsifiable hypothesis that an agent that reverses molecular neuroplasticity deficits in animal models should exhibit not only clinical effects on depression, but also correlated, simultaneous reversals of impairments at each level of analysis (Table 1). While some of these markers may be quantifiable in animal models, allowing for greater experimental controls (e.g., neural networks; cognition), others may be unique to humans (e.g., information processing; self-report). The use of a rapid-acting agent may be particularly beneficial in human studies, because the influence of many environmental and situational confounds inherent to human research are temporally contained due to the rapidity of ketamine's effects. However, ketamine research, like most pharmacological research, has focused largely on (a) molecular effects in animal models or (b) symptom-level effects in human patients. While molecular neuroplasticity effects are well-described in rodent models, attempts to extend molecular findings to humans (e.g., BDNF and synapse levels) have yielded inconsistent results[3], in no small part because of the difficulty of assessing these endpoints in the living brain, the tissue of interest. The cognitive, information processing, and neural network domains offer relatively untapped opportunities to integratively understand how enhanced neuroplasticity might ultimately translate to a profound shift in human experience, i.e. rapid depression relief.

Preliminary findings on ketamine's effects on neurocognition are consistent with the proposed model of neuroplasticity, suggesting clues as to how ketamine's rapid clinical and neuronal/molecular effects might manifest in other domains.

Neural networks:

fMRI investigations in depressed patients have linked ketamine's antidepressant effects to increased connectivity between mPFC and striatum[123], between lateral PFC and subgenual ACC[124], and to increased global connectivity between the PFC and the rest of the brain[55]. Convergent data show increased PFC glucose metabolism 24-hours post-ketamine[125,126], increased fMRI PFC activations acutely (during infusion itself)[127], and decreased limbic responses to angry (relative to happy) faces among ketamine responders[128]. Increased connectivity between the default mode network (DMN), which encompasses the medial PFC, and the insula have also been reported in depressed patients 2 days following ketamine, suggesting sustained normalization of the DMN's relationship to other networks[129].

Cognitive function: Two studies in rats[130,131] extend molecular findings in animal models to behavioral indices with possible relevance to cognitive flexibility in human patients. Following stress, rats randomized to ketamine (compared to saline) exhibited enhanced cognitive flexibility, as indexed by improved set-shifting task performance. In small, uncontrolled samples, convergent findings in depressed patients further suggest cognitive flexibility on objective cognitive tests improves acutely following ketamine[132,133].

Affective information processing:

Ketamine rapidly induces flexibility in implicit representations of self on the Implicit Association Test[134,135], and these shifts correlated with self-reported symptom improvements[110], suggesting that ketamine can immediately impact the structure of implicit mental representations relevant to one's concept of self, a core form of cognitive bias in depression. Although in a separate study, ketamine failed to illustrate a similar impact on attentional bias towards negative cues[128], the use of a reaction time measure (the dot-probe task) with notoriously poor psychometric properties[136–138] may have impeded the ability to sensitively detect changes over time.

Further integration across multiple markers of plasticity is needed to build support for an integrative model, as highlighted by the small number of direct "integration" links in Table 2. Of note, to accurately test for relationships in individual differences expressed across patients with correlational and mediational investigations, larger sample sizes are likely required relative to those necessary simply to establish the antidepressant efficacy of ketamine. Ongoing work in depression (e.g., R01MH113857;) aims to comprehensively characterize and link ketamine's depression-relevant effects across molecular, neural network, cognitive, implicit processing, and symptomatic levels of analysis in human patients, in the hopes of establishing a multi-domain neuroplasticity signature.

Testing predictions of the integrative model: Experimental manipulation at each level

In addition to manipulating molecular neuroplasticity targets (e.g., pharmacologically), a complimentary approach is to evaluate the causal influence of each posited form of plasticity by manipulating it directly (e.g., through mechanistic intervention; see Table 2:'Causality' for specific examples and evidence base) and observing its influence on clinical depression and all other levels of analysis. Leveraging RCT designs and explicit tests of 'target engagement' (to validate that the targeted neural, cognitive, or information processing manipulation was successful), this approach has the potential to distinguish causal influences on depression from depression correlates and to build support for a causal chain of neuroplasticity decrements leading to depression symptoms.

Generalizability and Transdiagnostic Relevance

Though the current review focuses on depression, it is notable that chronic stress is a risk factor for virtually all psychiatric conditions[139]. Likewise, the neural, cognitive, information processing, and psychological patterns discussed above have broad transdiagnostic relevance, particularly with respect to other disorders of negative affect (e.g., anxiety, trauma-related conditions)[140]—that likewise respond to pharmacologic interventions with plasticity-enhancing properties[141,142]. Equally noteworthy, however, is the marked heterogeneity of depressed patients, which is evident at the neural network[143,144], cognitive[145], information processing[145,146], and clinical[147] levels, and may help to explain the fact that no known intervention strategy is effective for all depressed patients. Rather than assuming a unitary etiology, and a correspondingly uniform pathway to recovery from

depression, a focus on establishing correlations across levels of analysis—both before and after administering plasticity-enhancing interventions—will help to clarify the degree to which an integrative neuroplasticity model may be relevant to some individual forms of depression and negative affect, but not others[140].

Conclusion

Neuroplasticity, or the brain's capacity to flexibly adjust and reorganize itself in response to a changing environment, is a fundamental contributor to adaptive functioning. Impairments of neuroplasticity often characterize disorders of negative affect including depression[3,4] and multiple efficacious therapies often reverse such deficits[10,148–151]. Our review highlights conceptual convergence of findings across relatively disparate literatures in basic neuroscience, cognitive science, and clinical psychology. Direct empirical links remain quite preliminary (Table 2). We hope to stimulate future studies with a broader integrative focus to empirically elucidate the intermediary mechanisms that allow neuronal and molecular changes at the cellular level to propagate up through a complex, circuit-based neurocognitive system. Ideally this work will suggest new treatment avenues to provide relief from pervasive, chronic, inflexible, and debilitating patterns of mood and behavior. Such novel treatments might aim, for example, to synergistically target more than one form of plasticity deficit simultaneously through theory-driven, somatic-behavioral treatment pairings[152].

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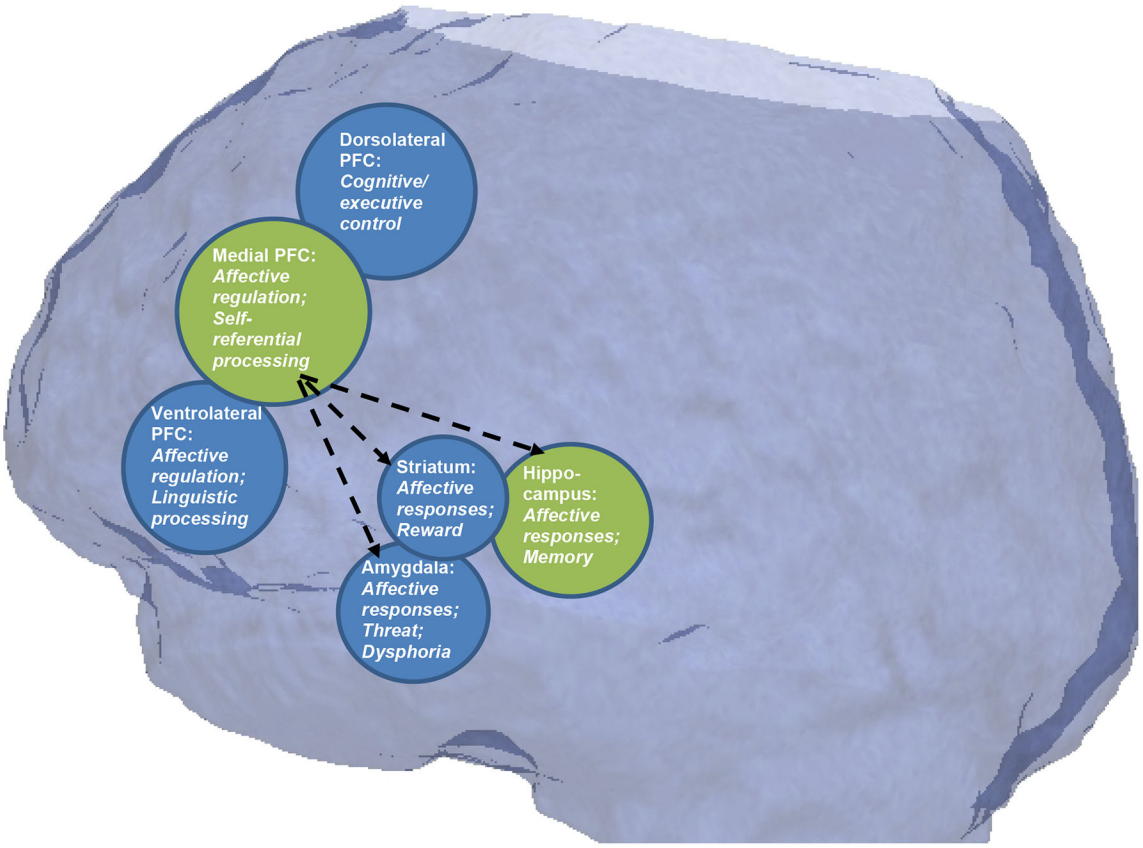

Figure 1:

Regions with prominent neuroplasticity deficits in animal models of depression[4,5] (in green) and functionally interconnected regions within a cortico-mesolimbic circuit relevant to mood regulation (blue). Some proposed functions of these regions with relevance in our integrative model are highlighted. “Medial prefrontal cortex (PFC),” as implicated in animal models, includes a number of subdivisions implicated in human depression including subgenual anterior cingulate cortex (ACC) and ventro- and dorso-medial PFC areas. Dashed lines represent primary hypothesized impairments in prefrontal cortex connectivity and top-down regulation of limbic regions, resulting in impairments in behavioral and cognitive flexibility across levels of analysis.

Table 1.

Neuroplasticity Markers Across Levels of Analysis

Level of analysis	Dysfunctional State	Treatment Goal State
Molecular/cellular	↓synaptic number and function, neuronal atrophy	↑synaptogenesis, ↑neurotrophic factors
Neural network	↓PFC-limbic circuit connectivity	↑PFC-limbic connectivity and ↑PFC regulatory control over limbic regions
Cognitive Function	↓flexibility, ↓cognitive control, ↓goal-directed inhibition/excitation of lower-order functions	↑flexibility and cognitive control, ↑goal-directed inhibition/excitation capacity
Affective Information Processing	rigid negative biases in implicit information processing (e.g., attention, memory, interpretations, self-representations)	unbiased and flexible information processing
Clinical/self-report	Perseverative negative thoughts, repetitive maladaptive behaviors, depression	novel positive thoughts/perceptions, diversified behavioral repertoire, euthymic mood, improved function/engagement

Table 2.

Summary of key findings supporting integrative neuroplasticity model

Plasticity marker	**Relevance: Key empirical findings linking marker to depression (see main text for details and citations)**	**Integration: Findings directly linking marker to other levels of analysis**	**Causality: Does manipulating marker lead to generalized depression relief?**
Molecular/cellular			
↓Synapse number and function ↓Neurotrophic factors	Chronic stress induces synaptic deficits in mPFC and hippocampus, which lead to depressive-like behaviors in animal models ↓prefrontal synapses in patients post-mortem Decreased BDNF in depressed patients	--	Approach: Intravenous ketamine Evidence: Strong support[12]
Neural network			
↓PFC-limbic circuit connectivity	Decreased PFC/limbic volumes, white matter integrity, intrinsic functional connectivity, and task-based connectivity in patients	↓PFC-limbic intrinsic[83] and task-based[42,43,105] connectivity linked to ↑negative attentional bias ↓intrinsic connectivity within limbic regions linked to ↑lassitude[153]	Approach: Neurofeedback Evidence: Preliminary support[154,155] Approach: Neuromodulation of PFC Evidence: Moderate-to-strong support[156]
Cognitive Function			
↓cognitive/executive control memory impairments (prospective memory deficits; overgeneral autobiographical memory)	Decreased executive functions Impaired and “over-general” memory recall	↓Self-reported cognitive control linked to ↑negative attentional bias[157] ↓Self-reported cognitive control linked to ↑depression severity via ↑rumination[158] ↑Overgeneral memory linked to ↑rumination and ↓executive function[159]	Approach: Cognitive control training Evidence: Preliminary support[75] Approach: Autobiographical episodic memory training Evidence: Preliminary support[160]
Affective Information Processing			
Attentional bias Interpretive bias Memory bias Biased self-associations Biased reward learning	Behavioral task performance supports the existence of each form of bias in depressed patients	Attentional bias: see above ↑negative biases in inhibitory control linked to ↑rumination[7]	Approach: Cognitive bias modification Evidence: Mixed/limited support[108] (possibly related to difficulties in robustly modifying biases with current approaches)[161] Approach: Evaluative conditioning of self-associations Evidence: Collateral/preliminary support[162]
Clinical/self-report			
Inflexible thought patterns Inflexible behaviors	Repetitive negative thinking patterns (e.g. rumination, depressive schemas); constrained behaviors (e.g., lassitude) reported routinely by depressed patients	Lassitude and rumination: see above	Approach: Cognitive therapy Evidence: Strong support[114] Approach: Behavioral activation Evidence: Strong support[119]