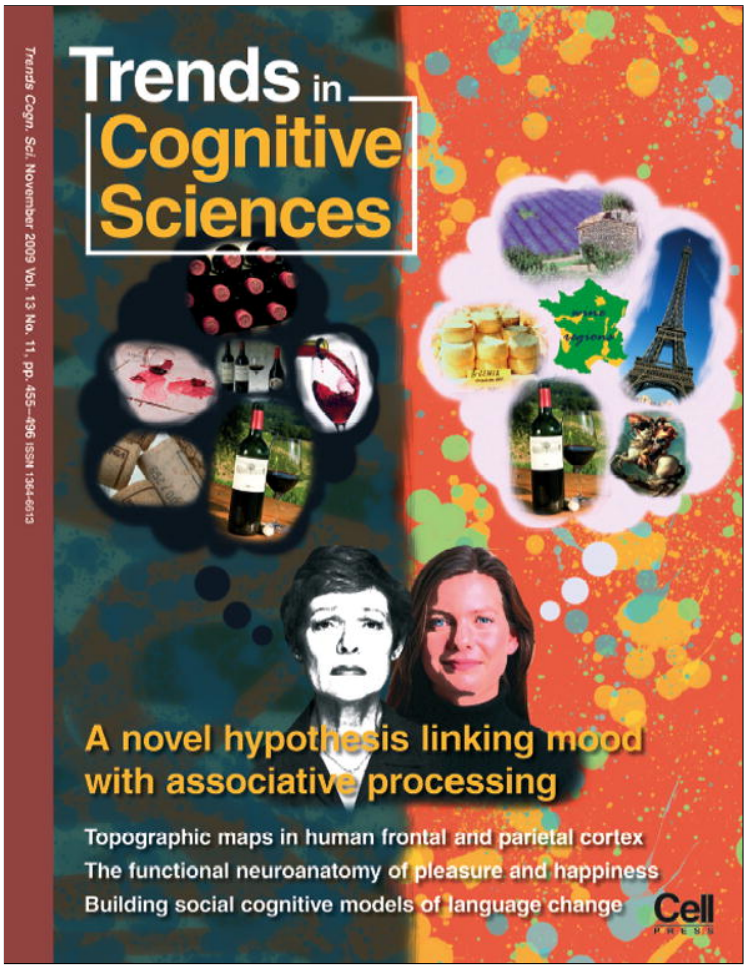

Opinion

A cognitive neuroscience hypothesis of mood and depression

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Although mood has a direct impact on mental and physical health, our understanding of the mechanisms underlying mood regulation is limited. Here, I propose that there is a direct reciprocal relation between the cortical activation of associations and mood regulation, whereby positive mood promotes associative processing, and associative processing promotes positive mood. This relation might stem from an evolutionary pressure for learning and predicting. Along these lines, one can think of mood as a reward mechanism that guides individuals to use their brains in the most productive manner. The proposed framework has many implications, most notably for diagnosing and treating mood disorders such as depression; for elucidating the role of inhibition in the regulation of mood; for contextualizing adult hippocampal neurogenesis; and for a general, non-invasive improvement of well-being.

Rationale for linking mood with associative processing

Mood has a direct impact on mental and physical health, ranging from depression and anxiety to cardiovascular disease, addiction, psychological resistance, cognitive performance, aging and longevity. Nevertheless, our understanding of the mechanisms underlying mood regulation is still limited. The crux of the hypothesis presented here is that mood is directly linked to how associative or inhibited are our mental processes. There is compelling evidence in support of one direction of this link: that positive mood results in broad associative activation of related concepts. Here, I propose that the reverse relation also exists, whereby broad activation of associations results in improved mood. This relation might stem from an evolutionary pressure to learn and explore many alternatives in parallel, possibly motivated by the increased release of neuropeptides with increased activation of associations. One function of such simultaneous exploration could be to support the constant need of humans to anticipate relevant outcomes. Therefore, the activation of associations might be beneficial for improving mood because associations afford the generation of predictions, and predictions minimize uncertainty, thus reducing anxiety and stress, which are both concomitants of mood disorders. The second mood-related benefit of broad associative activation is that associations prevent persistent rumination, another hallmark of mood disorders, by 'distracting' the thought process away from dwelling on a narrow, negative theme. Broad associative activation helps gain a broader perspective.

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Here, I synthesize existing evidence that collectively supports the proposed link between mood and associations and suggest testable predictions that are derived from the ideas outlined here. I also make several suggestions for therapeutic approaches that build on this theory and that could alleviate symptoms of major depression and, more generally, improve well-being through better mood.

Relevant aspects of associative processing

Our world consists of patterns that typically occur together (e.g. kitchens contain refrigerators, visiting a museum requires being quiet and showers are taken without clothes). These statistical regularities are encoded in memory as associations, linking related representations and co-activating them as necessary in subsequent encounters. The ability to associate a particular sensation (or perceptual feature, object, concept or emotion) with another is crucial for most aspects of mental functioning. In addition to their fundamental and widely studied role in learning, memory encoding and retrieval, problem solving, creativity, action and spatial navigation, associations provide the basis required for generating predictions [1]. When one encounters a novel situation, one extracts from memory an analogous situation with which one is already familiar, and applies the corresponding associative knowledge from memory to anticipate relevant aspects of the present, novel but similar, situation.

In the context of my proposal here, associations provide the vehicle with which thoughts advance from one representation to another. Central to the proposal is the distinction between narrow and broad associative activations. Narrow associative thinking, or rumination, refers to associations that surround a narrow focus (e.g. the context of my bad comment over dinner last night: what I said, what I should have said, the resulting facial expressions and verbal responses to it, possible future implications and so forth). Ruminative, narrow associative processing, as proposed below, might stem from excess prefrontal inhibition (Figure 1a). Broad associative activations, by contrast, involve more remote associations and, crucially, activate associations that make thought processes advance from one context to another smoothly (Figure 1b), thereby minimizing rumination (e.g. 'in spite of that miserable comment, dinner was really tasty; never tried the combination of figs with prosciutto before; need to go grocery shopping tomorrow').

Recent studies using human neuroimaging looked at the cortical mechanisms mediating contextual associations in particular [2–4]. The associations that tie items that share

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the same context consistently activate three main cortical regions: the medial temporal lobe (MTL), the medial partial cortex (MPC) and the medial prefrontal cortex (MPFC) [3]. This contextual association network shows a striking overlap with the cortical network termed the 'default network' [5], as we have shown recently [4]. The default network is believed to subserve the mental processes that occur in the brain when an individual is not engaged in a specific goal-oriented task [6,7]. This overlap between the default network and the network subserving the associative processing of contextually related information is taken as the cortical manifestation of the older idea that associative processing is a crucial element of natural thought [4]. In other words, associative activations provide the building blocks that enable thought processes to proceed from one topic to another. Notably, other tasks, including hedonic processes, reward-related processes and affective processes, also activate parts of this associative network. This common activation by different processes has been interpreted as reflecting the fact that these processes all rely on associative activations at their core [4].

Contextual associations and mood are linked here directly first by noting recent reports that patients with depression tend to ignore global context [8]. Such findings make sense when one considers the tendency of such individuals to ruminate on a single, usually negative, theme. The link to the single-track, narrow mode of thinking in depression is strengthened further by findings showing that the contextual associations network, including the MTL, MPC and MPFC, functions abnormally in these patients [9,10]. Finally, the link between depression and contextual associations might further be supported by recent findings of adult neurogenesis in the MTL in the context of depression treatment.

Positive mood promotes associative processing

Human subjects in positive mood provide more unusual associates to neutral words, compared with subjects in negative or neutral moods [11]. In addition, positive mood facilitates creative ingenuity in problem solving [12], and false memory, which is presumably a result of associative activation, is minimized in negative mood [13].

A parallel to the conclusion that positive mood promotes associative thinking is the finding that positive mood is accompanied by a wider attentional 'spotlight,' whereas negative mood can be characterized by a more focused type of thinking [14]. For example, when subjects need to accomplish memory or categorization tasks, those in happier mood utilize available global information, whereas the attention of participants in a sad mood is focused on more local properties. Similarly, positive mood and optimism are directly associated with a global processing bias in visual tasks, whereas a local bias is observed for people in negative mood or with depression [15]. Negative mood might signal the potential presence of threat and, thus, might elicit a more focused mode of processing. Indeed, dangerous environments also have the same effect on the scope of attention as that of negative affect [16]. The influence and functional merits of positive emotions, by contrast, have been framed as expanding thought repertoire (i.e. scope) in a host of dimensions within a comprehensive related framework termed 'broaden-and-build' [17].

Finally, associative processing has been linked with the ability to imagine future events and to predict upcoming information [1]. Therefore, the fact that foresight is impaired in depressed individuals [18] provides encouraging support to the idea that associative activation and mood are directly related.

The proposal here is not only that mood broadens associations and attentional scope, as reviewed above, but that the opposite direction of influence also exists: associative thinking can promote positive mood. This direction of influence (associative cognition→improved mood), as discussed next, could have profound implications for the treatment of mood disorders.

Associative processing promotes positive mood

Rumination, the preoccupying, self-focused thinking pattern that is commonly a concomitant of mood disorders [19] could be seen as the functional opposite of broad associative thinking, given its narrow focus. If rumination involves associative processing, such associations do not advance far beyond the main focus of rumination (Figure 1a). Inducing rumination even in healthy individuals results in a negative mood [20]. Interestingly, it has been suggested that the focus of rumination does not necessarily have to be negative in nature [21,22], so it is possible that the process of rumination, rather than exclusively its content, contributes to the negative mood. However, to demonstrate unequivocally that it is the rumination process, and not necessarily the content, that affects mood, one would have to show that ruminating on a positive thought also elicits negative mood. The problem is that, by definition, within the framework proposed here, ruminating on positive content for long periods is impossible because the positive content will make the individual drift and associate broadly. Nevertheless, independent of the interesting question of process versus content, it is proposed here that inducing the opposite of rumination (i.e. frequent, broad associative activation) will elicit a positive mood.

Rumination appears to be a major vulnerability factor for negative mood associated with major depression but also with other disorders, including post-traumatic stress disorder (PTSD) [23], anxiety, and obsessive-compulsive disorder (OCD). In fact, given the overlap between rumination and worry, and the prevalence of both [24], the present hypothesis could be relevant across most psychiatric disorders.

One effective therapy in treating stress disorders involves shifting attention from an upsetting stimulus to something relatively neutral [25]. However, merely shifting the focus of attention does not necessarily activate broad associations and, thus, might lose its efficiency of distracting the ruminating mind as a long-term remedy. Indeed, in accordance with the hypothesis presented here, distraction as a soothing technique is most effective when the identity of the distracter varies frequently [26,27]. One can therefore consider frequent, broadly associative thinking as providing a higher rate of distraction and, thus, fewer opportunities to ruminate and dwell on a negative thought.

Interestingly, it has been reported that speed of thought, as manipulated by paced reading, has a direct influence on mood [28]. Specifically, these studies suggest that reading faster can make one feel more positively, regardless of whether the content of the text is positive or negative. Reading causes the activation of concepts and faster reading activates more concepts, which could be seen as analogous to the massive activation in broad associative activation (i.e. more concepts activated per time unit). Therefore, although this finding could be attributed to the mere speed of 'mental motion' [22], or perhaps to the fact that a mentally demanding reading activity could serve as a powerful means of distraction from rumination, it could also provide support to the proposal outlined here, that increased associative thinking elicits increased positive mood. The present framework goes beyond previous reports in that it describes a mechanism, and this mechanism integrates cognition, neuroscience and clinical findings. The result is a framework within which other proposals (e.g. Refs [22,28]) appear to fit naturally.

Neural elements linking mood and associative processing

Converging evidence for the proposed framework comes from research in neuroscience and psychiatry. First, that successful treatment of depression appears to be conditional upon a concomitant volume increase in the adult hippocampus [29]. Second, that electrically stimulating prefrontal regions implicated in associative processing alleviates depression symptoms [30].

Associative processing and the ability to learn associations between previously unrelated items have been attributed primarily to structures of the MTL, particularly the hippocampus [31,32], and the parahippocampal cortex [4,33]. Several recent studies have demonstrated both functional disturbances and volume reduction of the hippocampal formation in depression [34,35]. Importantly, the severity of depressive symptoms is directly increased by such hippocampal structural disturbances [36], as well as by a decrease in hippocampal activity [37]. Additionally, successful antidepressant treatment can halt the progression of hippocampal damage [35], and is associated with recovery of hippocampal volume [38]. These results demonstrate the close relationship between depression and the functional and structural integrity of the MTL.

One of the most effective medications for treating depression relies on selective serotonin reuptake inhibitors (SSRI), such as fluoxetine (e.g. Prozac). In recent years, it has been observed that SSRIs have a direct influence on adult neurogenesis [39], particularly in the dentate gyrus within the hippocampus [35,40]. Importantly, serotonin has also been shown to have a central role in learning and memory formation [41], which is widely believed to be mediated by the MTL and to rely on associations.

Adult hippocampal neurogenesis is still a new and controversial topic. Nevertheless, the possibilities, especially for our understanding of mental disorder, are profound and thus warrant further attention. There is accumulating evidence to suggest that hippocampal neurogenesis is not merely an epiphenomenon of the chemical effect of SSRIs, but has a causal effect on the success of SSRI treatment: The newly generated neurons seem to have a direct effect on the state of depression, whereby successful antidepressant treatment is conditional upon successful hippocampal neurogenesis. Indeed, blocking hippocampal neurogenesis substantially reduces the efficiency of antidepressants [29].

Computational modeling work [42] shows that such neurogenesis could be crucial for establishing new contexts for behavior in memory and such contexts are based on associative representations and activations [4]. Indeed, associative long-term potentiation (LTP) can be induced in new neurons more readily than in older neurons [43], and the magnitude of LTP can be modulated by serotonin [44]. Together, these converging findings provide a potential mechanism for the increase in associative processing with neurogenesis and SSRI-based therapy (Box 1).

A second line of research that is related to the proposal presented here concerns findings that indicate that electroconvulsive therapy (ECT) and transcranial magnetic stimulation (TMS) exhibit anti-depressant effects [45]. How these treatments exert their effects is still unknown. Recently, Mayberg and colleagues [30,46] demonstrated that electrically stimulating the deep Brodmann area 25 (BA 25; Figure 2a) can alleviate the symptoms of major depression patients. Area 25, the subgenual cingulate, is situated in the MPFC, which is activated in associative cognitive tasks (Figure 2b). One mechanism by which such deep brain stimulation (DBS) in MPFC can affect depression symptoms might be through the regulation of inhibition. Memory consists of a web of representations that are connected with each other, directly or not. Although this makes for an efficient framework for encoding and retrieval, it is crucial that the activation of one mental representation (e.g. a chair, when one sees an image of a chair) would not result in the exraneous activation of representations that are irrelevant in the specific context. Inhibition is proposed to have the critical role of limiting the extent of connected representations that are activated at a given instance (e.g. seeing an image of a chair would activate 'chair,' 'table' and perhaps 'legs,' but should not activate 'chicken legs'), thereby giving rise to associations and predictions that are most relevant. In the context of inhibition and mood, an abnormally activated MPFC, as in depression [47], can result in over-inhibition from MPFC to MTL, which might then significantly constrain the scope of associative activation in MTL [48]. Excessive inhibition from MPFC could explain the inability of depressed patients to disengage from debilitating rumination (Figure 1a). Indeed, inhibitory dysfunction can exacerbate depression through rumination [49]. DBS might therefore operate by bringing MPFC back to its normal level of activity (Figure 1b), which brings back inhibition to a level where MTL can resume broader associative activation.

It is particularly interesting that the pattern of brain activity typically observed at 'rest' (i.e. default brain activity) in healthy individuals differs in patients with depression symptoms. The MPFC and the neighboring anterior cingulate cortex in particular exhibit abnormal activity during periods of 'rest' in individuals with depression compared with those without [50], and activation in these regions appears to predict treatment success [51].

Box 1. Qualifications regarding hippocampal neurogenesis and depression

First, the loss of neurogenesis appears to be neither sufficient nor necessary for developing depression symptoms, but neurogenesis can nevertheless be crucial for treatment success. Within the framework proposed here, one can imagine a thinking pattern that is broadly associative because the infrastructure that affords broad associative processing is in place, and can remain so even without neurogenesis. However, for an individual suffering from depression, such infrastructure needs to be rebuilt, which can only be done with new neurons and new connections. Furthermore, the birth of new hippocampal neurons will exert no behavioral and clinical influence if these neurons do not integrate and survive; neurogenesis without the associative activity that will promote the survival of the new neurons will not be sufficient for alleviating the symptoms of mood disorders, according to this proposal. Therefore, in thinking about the reciprocal relation between neurogenesis and associative activation, neurogenesis can be seen as providing the medium, but this needs to be used by broadly associative activation to survive and generate the webs of associations that mediate the non-ruminative activation required for a healthy mood.

Second, neurogenesis is not always beneficial, as is the case in temporal lobe epilepsy [75], where new cells might migrate incorrectly. Third, depression might be accompanied by cognitive impairments that might go beyond associative processing. For example, the MPFC has been implicated in thinking about self and in reward-related processing. These other functions nevertheless rely on associative processing; for example, self-reflection is associated with rumination and reward relies on learned associations. Finally, this is not to suggest that all types of depression can be treated in the same fashion [76], or that they all stem from hippocampal and/or prefrontal processes.

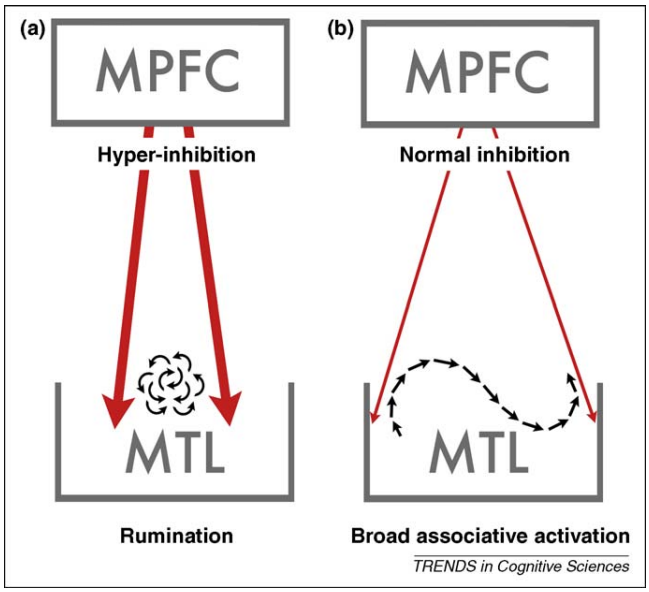

Figure 1. Rumination versus broadly associative thinking. **(a)** The thought pattern typical of mood disorder involves rumination around a narrow focus. Even if this thought pattern is associative, it is limited in scope. Such constrained thought is proposed here to stem from hyper-inhibition from the MPFC to the MTL. **(b)** The thought pattern in the brain of individuals without mood disorders is characterized by a broadly associative activation that, although still affected by inhibition signals (for functional guidance), can seamlessly disengage from one focus and advance to another.

Furthermore, the structure, function and connectivity of the same default/associative network (Figure 2b,e) are compromised in depression [52,53] and the integrity of this network is improved with antidepressant-related clinical improvement [53].

A therapeutic approach that promotes activation of those regions via intense associative processing can be seen as a cognitively generated analogue of DBS and, thus, might elicit similar mood benefits. Although cognitive endogenous triggering of associations and regulation of inhibition is likely to be less intense than direct electrical deep stimulation, it is expected to be more focused and to encompass the entire network of interest. In addition, DBS is primarily applied in cases of severe major depressive disorder (MDD), when most other methods have failed. It is possible that, for less severe cases of depression, a reduced intensity of stimulation in the same area will suffice for observing significant symptomatic improvement.

Further implications for therapy and testable predictions

Existing cognitive-behavioral therapy (CBT) techniques approach mood disorder by aiming to help patients first recognize thoughts that accompany their negative emotions, to distance themselves from these thoughts, and then encourage the patients to question the validity of the beliefs embedded in their maladaptive thoughts [54,55]. CBT methods improve symptoms for certain

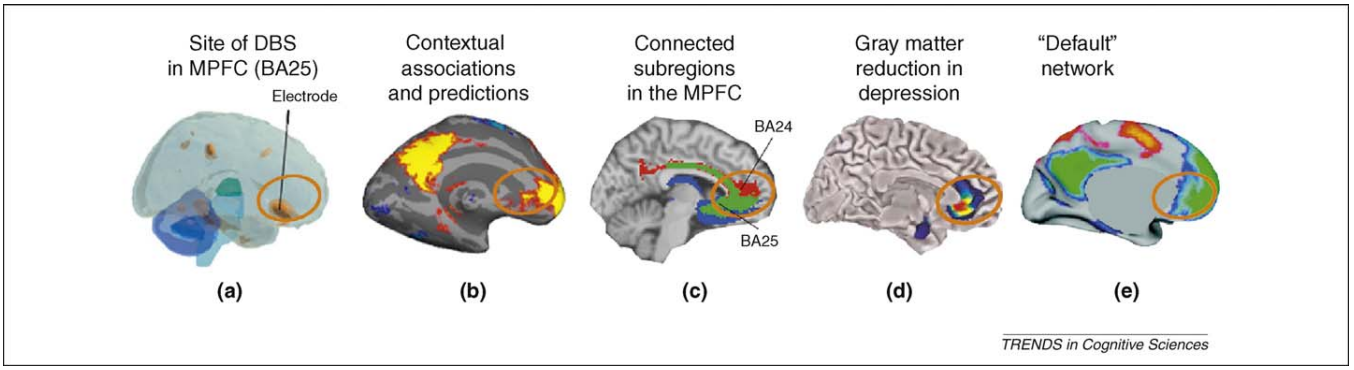

Figure 2. Converging activations in MPFC. The same MPFC region that is stimulated by DBS to treat severe depression and where activation is most indicative of successful treatment **(a)** is strongly active in studies of context-based associative predictions **(b)**. **(c)** Anatomical support for the direct and extensive connection between BA 25 and the MPFC region activated by contextual associations has been reported previously [71]; further support comes from using population maps of probabilistic tractography of strongly interconnected MPFC regions [73]. **(d)** The same region (MPFC) shows reduced gray matter in patients suffering from depression compared with patients without depression [46]. **(e)** The default network [74] shows striking overlap with the same network that mediates contextual associations and predictions (b) [4]. Recruiting this MPFC region by cognitive means, as in **(b)**, could regulate inhibition and retrain the natural tendency to engage in broad associative activation, which is compromised in mood disorders. Modified, with permission, from Ref. [72] **(a)**. Reproduced, with permission, from Ref. [73] **(c)**, Ref. [46] **(d)** and Ref. [74] **(e)**.

depression patients [56] and even more so when conducted in conjunction with antidepressant medication treatment [57]. CBT has also been shown to modify brain activation patterns in patients with depression [58], with some overlap with the modifications caused by antidepressant medication [54]. The aims of CBT can be seen as teaching patients to see things in a broader perspective and to incorporate more context (and thus more associative processing) into their analysis of emotional information, an approach that could be explained by the mechanism put forth here. Nevertheless, CBT requires a high level of functionality and introspection from patients, and it is unclear whether this method is feasible and effective for the same large patient population as antidepressants. The proposal presented here gives rise to a potential treatment method that would promote the (not necessarily conscious) acquisition of mental habits of broad associative activation and a cognitive-driven reconstruction of the underlying cortical network. Such an approach could increase the efficiency of non-invasive therapy, elicit a positive response in a wider portion of patients and demand considerably less psychotherapeutic introspective effort from patients.

Another advantage of promoting broad associative activations as part of a therapy is that it does not require patients to suppress specific thoughts actively, but rather simply increases the shift from rumination. Explicitly attempting to suppress a specific thought is considerably harder than anticipated, therefore suppression is not effective for alleviating depression, and might even be counterproductive [59]. Fostering a thinking pattern that is more associative in nature instead will divert thought to other themes more readily. Methods such as meditation require trainees to 'observe thoughts and let them go.' In a healthy mind with broad associative activations, the process of 'letting go' is expected to occur naturally. In this context, no claims are made here about whether the pattern of thought can be controlled voluntarily, or whether it is automatic. The issue of control is interesting and has already received considerable attention [60], but it is less relevant in the present proposal. The premise of the therapeutic potential of this proposal lies on the idea of restoring the cortical infrastructure that regulates inhibition and enables one to broadly associate and disengage from ruminations in a natural manner. The hypothesis is that when this infrastructure exists, thinking is more associative and is independent of voluntary control.

Similar proposals can be made for other conditions that involve mood disorders. For example, patients with PTSD show abnormal activation in the same regions where microstimulation shows benefit for depression symptoms, area BA 25 (as well as BA 24) [61]. PTSD can be seen as a form of rumination, where associative memory retrieval is focused narrowly on a traumatic memory with a limited ability to shift away from this focus. One might therefore suspect that a similar approach for promoting broad associative thinking as a means of disengaging from rumination could also be helpful for PTSD patients. Similarly, this approach is predicted to prove beneficial in stress and anxiety disorders, phobias and possibly even in normal aging.

The present hypothesis gives rise to a counterintuitive prediction that attention deficit hyperactivity disorder (ADHD) patients, whose mental processes tend to be doing the exact opposite of ruminating, are expected to have a more positive mood than that of individuals without ADHD. There has been little research on mood effects in ADHD, and such measurements might be influenced by multiple factors that could counteract each other. Nevertheless, existing research indicates that children with ADHD tend to be relatively more positive than control subjects, as reflected, for example, by affective valance [62], and positive illusory bias [63]. Furthermore, the hippocampus of ADHD patients is of a significantly larger volume compared with that of controls [64], and, although acute depression is typically associated with an enlarged and hyperactive amygdala [65], the amygdala of ADHD patients is smaller that that of controls [64]. With the links made here between broad associative processing, its inhibition and mood, ADHD could be attributable, at least in part, to deficits in inhibition rather than portrayed exclusively as an attention disorder.

Previous findings show that patients with depression are deficient in foresight and future-related thinking [18]. Therefore, one would predict that successful treatment of mood disorders will increase patients' foresight and ability for future-oriented mental operations, such as planning and mental simulation.

Our understanding of mood manifestation in the brain is largely lacking, but a reasonable hypothesis might be that it involves the release and binding of neuroendorphins. If activating certain neural paths results in an increased release of neuroendorphins, one can see how ruminating on the same theme for a long period exhausts the release of such rewarding opioids from the repeatedly active neurons (and why repetition is often boring), whereas activating broad associated representations and pathways that have not been activated recently increases rewarding activations (as well as encourage one to attend to novelty in the environment). This aspect of the proposal, that the brain might use the release of neuroendorphins as an incentive to activate associations to promote learning and minimize uncertainty, is speculative and requires further interdisciplinary investigation. Nevertheless, recent theoretical and empirical work suggests that a MTL region similar to the one shown to be activated by contextual associations (i.e., the parahippocampal cortex) shows increased fMRI activation for pictures that participants find as pleasant [66,67]; this area might be at the top of a hierarchy of increased concentrations of opioids. Indeed, the highest levels of opioid binding have been found in the orbital MPFC and in the MTL [68], cortical nodes of the network highlighted in this proposal.

Finally, new neurons that are born in the adult hippocampus must be integrated with existing networks to survive. That SSRIs help only a subset of patients but not others should be examined in parallel to what other habits these patients have. It is possible that those for which SSRIs are not effective do not engage in activities that promote the survival of new neurons, such as intense learning and other forms of associations-based mental enrichment [69,70]. In the broad associative framework presented here, new neurons are supposedly born as a

result of demand and usage and, thus, their chances of integration and survival are increased.

Concluding remarks

Associations are inherently crucial for learning, and the healthy brain might be motivated to learn by a consequential mood reward. As has been proposed and shown in the past, associations are also crucial for the generation of predictions [4]. Being able to minimize uncertainty with the generation of association-based predictions is a most effective means for improving chances of survival. Therefore, activating associations broadly and frequently, while still being able to focus more narrowly when necessary, could provide a mechanism that promotes survival and progress. When using this mechanism 'as intended', one is rewarded with a positive mood.

The activation of broad associations, as predicted here, makes mood more positive. Ruminating, by contrast, makes mood negative. It might be possible that the act of rumination is by itself sufficient for eliciting a negative mood, independent of whether the focus of this rumination is negative (e.g. a bad memory). So why does one not become depressed when concentrating on driving, reading, or meditating? One crucial difference might be the duration of such attentive focus. Rumination that is associated with depression tends to have a longer duration than everyday, emotionally neutral tasks usually entail. Perhaps more importantly, however, this question helps sharpen the distinction between rumination and a narrow scope of attention: the narrow focus of attention while working towards a goal still advances over time (e.g. during writing), whereas the narrow attention associated with rumination remains focused on the same topic.

In summary, the proposal presented here outlines a cognitive neuroscience framework with which to understand mood. This framework could provide the foundations for future development of non-invasive methods for treating mood disorders, whereby the training and restructuring of the ability for broad associative thinking can elicit improvements that range from structural modifications to mood and behavior (Box 2).

Box 2. Questions for future research

- There are several relationships that have been alluded to here, where the directionality and causality of the relation is as yet unclear: Does depression cause hippocampal and MPFC damage, or is it the structural disruption in MPFC and MTL that causes depression? Do more associations generate more new hippocampal neurons, or do more neurons afford more associations? The questions of directionality and causality will need to be answered; however, for the purpose of developing an effective, non-invasive approach to therapy, it is assumed that addressing and improving one aspect of these facets will also bring about improvement in the other facets. In other words, it is proposed that rebuilding the ability of the brain to activate broad associations continuously and to resume a normal level of prefrontal inhibition will reduce rumination, emulate DBS internally, elicit hippocampal restructuring and, ultimately, help mood disorders.
- One strong prediction that stems from this framework and that can be readily tested is that rumination and negative mood are associated with excessive inhibition from MPFC to MTL, as proposed in Figure 1 (main text). Similarly, ADHD, and possibly schizophrenia (also accompanied by hyper-associativity), are accompanied by insufficient inhibition from MPFC to MTL.
- The role of the MPC is largely under-explored. Given the extent and consistency of its activation, however, it is reasonable to expect that it is playing a central role in mood in particular, and in cognition more generally.
- To what extent do individuals experience associative processing as a phenomenal state or, instead, are non-conscious of its operation? This question has theoretical as well as clinical implications.
- Discussing neurotransmitter systems, such as the dopaminergic and the serotonergic, was beyond the scope of this article, but there is little doubt that they both have central roles in mood regulation. These systems have attracted much interest, resulting in groundbreaking findings, but the question of what their exact role is in mood remains. In the context of the framework proposed here, it would be interesting to study how the dopaminergic and serotonergic systems interact with the cognitive network responsible for associative activations. With regard to the dopaminergic system, for example, it is curious that some individuals see dopamine as the 'pleasure molecule,' providing a pleasant feeling of reward and motivating with reinforcement, whereas others see dopamine as central to anything related to predictions, reward prediction and prediction error. But there is no satisfactory link between the two functions: how is the same system responsible for both predictions and for pleasurable feeling? Considering the role of associations-based predictions in positive mood, as proposed here, could provide such a bridge.

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