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EDITORIAL REVIEW

Recurrence in major depressive disorder: a neurocognitive perspective

O. J. Robinson and B. J. Sahakian*

Department of Psychiatry and Behavioural and Clinical Neuroscience Institute, University of Cambridge School of Clinical Medicine, Addenbrooke's Hospital, Cambridge, UK

Depressive disorders are amongst the leading causes of disability and mortality worldwide and, as such, it is predicted that by 2010 only cardio-ischaemic disorders will provide a greater burden. In addition to the sizable emotional, individual and social burden, depressive disorders cost an estimated US$83.1 billion per year in the United States alone. In spite of effective treatments, a large proportion of sufferers go on to experience recurrences. With successive recurrences, the likelihood of subsequent episodes increases. Despite this, research to date has tended to focus on first episodes or else has not distinguished between episodes. This editorial review highlights a number of differences between first and recurrent episodes which, in turn, recommend more longitudinal, recurrence-oriented, treatments. We also examine the findings from acute tryptophan depletion studies which, it is speculated, help to understand the differences between successive episodes. The overall aim, however, is to highlight the importance of recurrence in depression and to stimulate debate.

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Introduction

Having suffered from a first episode of major depressive disorder (MDD) a large number of sufferers experience recurrences. Each recurrence seems to then increase the likelihood of subsequent recurrences (Kendler *et al*. 2001). In some patients, therefore, depression becomes a long-term, cyclical condition.

A large body of work has focused on the changes that occur in depression. Of these the most immediately obvious is in (1) mood. This is accompanied by a change in (2) cognitive performance which includes 'negative biases'. Additional abnormalities in (3) monoaminergic neurotransmission [serotonin (5-HT), dopamine (DA) and noradrenaline (NA)] are also found alongside (4) a dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis (de Kloet *et al*. 2005). These changes are associated with all episodes of depression.

The literature is sparse with specific regard to recurrent episodes, but the studies that do exist seem to suggest that these changes return but in an increasingly pronounced manner. Rumination, negative biases, memory problems and cortisol release all show relative increase with successive episodes whilst sleep efficacy and social interaction ability diminish (Thase *et al*. 1995; Bouhuys & Sam, 2000; Nandrino *et al*. 2002, 2004; Fossati *et al*. 2004; Sher *et al*. 2004). This pattern of decline may continue until at least the ninth episode (Kendler *et al*. 2001).

This alteration in symptom severity is accompanied by an alteration in the factors that trigger an episode. A consistently implicated trigger of depression is that of environmental stress. Stress can induce negative mood, provoke cognitive change, reduce cerebral 5-HT (Russo *et al*. 2003) and increase HPA axis activity and therefore provides a common link between the different symptoms. These stress-induced changes are normally temporary but it is thought that following chronic or extreme stress, they can persist and an episode of depression is experienced (de Kloet *et al*. 2005). A first episode of depression therefore tends to be triggered by a 'major life event' (such as bereavement). Subsequent episodes, however, tend to either be triggered by milder stressors or become totally independent of stress (Lewinsohn *et al*. 1999). This indicates a pattern of reducing stress threshold with each successive episode which might, in turn, explain the increasing risk of recurrence. The concept of 'kindling', in which the first episode is said to leave behind a residue that makes subsequent episodes more likely, has been proposed to explain this

* Address for correspondence: Professor B. J. Sahakian, University Department of Psychiatry, Box 189, University of Cambridge, Addenbrooke's Hospital, Cambridge CB2 2QQ, UK.
(Email: ojr23@cam.ac.uk)

observation (Segal *et al*. 1996; Post & Weiss, 1998; Kendler *et al*. 2001). Such a residue might also explain the existence of symptoms in remission in some patients.

Can acute tryptophan depletion (ATD) reveal 'kindling'?

ATD studies in which cortical 5-HT levels are reduced through the dietary reduction of tryptophan may provide experimental evidence for this kindling effect. ATD has been shown to induce cognitive biases and HPA axis dysregulation in healthy people (Murphy *et al*. 2002). However, clinically significant negative mood following ATD is found only in recovered depressed individuals (Booij *et al*. 2002). Is there, therefore, something that occurs during an episode of depression that causes negative mood to be evoked by ATD and, furthermore, can this help to explain the kindling effect?

Acquired 'associations' between depression-related changes

Our overall speculation is that when stress triggers abnormalities in mood, 5-HT function, HPA axis and cognitive function, *associations* form between the specific *neural substrates* underlying these changes. Evocation of one will then result in evocation of others. This could then explain why subsequent episodes of depression are easier to trigger. It may also explain why ATD-induced clinically significant negative mood is only found in recovered depressed individuals.

This concept of association is supported by a range of theories of emotion and depression. The '*two-factor model*' (Schachter & Singer, 1962) of emotion provides initial support. It describes how individuals can experience the same physiological manipulation (i.e. an adrenaline shot) differently (as, for example, elation or anger) depending upon their current context (a room, for example, with either an entertaining or irritating stooge). This therefore supports the notion that the same ATD manipulation can evoke negative mood in some individuals but not others.

The '*somatic marker hypothesis*' suggests how the negative mood could be evoked (Damasio, 1996). It posits that in emotional processing, somatic and neural states contribute to an overall pattern of neural activity (the 'body loop') which is then consciously perceived as a feeling or mood. This neural pattern, which initially requires input from both the brain and the body, can then come to be evoked solely by the brain. This brain-only activity is termed the 'as-if body' loop. ATD-induced negative mood may therefore be evoked via an 'as-if body' loop that mimics the 'body loop' found in depression.

'*Associative learning theory*' then describes how two events (be they stimuli or patterns of neural activity) can become paired by simply occurring at the same time (Dickinson, 1981). A theoretical extension is that the negative mood (and the associated 'as-if body' neural activity) could become paired with the low 5-HT physiology (and associated neural activity – see below) simply by virtue of their stress mediated co-occurrence. If this occurred, then each one would be able to independently activate the other. Such associations have also been shown to strengthen with successive pairings which could explain the pattern of increasing vulnerability with successive episodes.

In addition to this, once a negative mood state has been established, *state-dependent recall* of memories established in the depressed state may then result in re-evocation of further negative memories and mood (Weissenborn & Duka, 2000).

In summary, therefore, our hypothesis is that the different symptoms of depression involve different patterns of neural activation that become associated during a first episode and that this, furthermore, could underlie the 'kindling' effect. Our hypothesis is supported by the suggestion of Teasdale & Dent (1987) stating that negative biases and depressed mood are initially independent but then become associated during a depressive episode. If it is accepted that cognitive biases and negative mood are associated with dissociable neural substrates then their mechanism of association may be the same as outlined above.

Neural substrate of the 5-HT–negative mood association

Low 5-HT and negative mood are likely to be associated with dissociable neural substrates. 5-HT is a neuromodulatory neurotransmitter – it can both directly activate neurones and alter their firing pattern. This means that neurons with 5-HT receptors will behave very differently in different 5-HT concentrations. Ultimately this will result in different overall patterns of neural activation on and off ATD. The distinct pattern of ATD neural activation is what can become associated with the ('as-if body') pattern of neural activation associated with negative mood. The end result is an ensemble pattern of activation which, when evoked by ATD, provokes negative mood.

Susceptibility to acquiring associations

Thus far the theory explains how ATD might evoke negative mood in recovered depressed individuals.

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However, *subclinical* mood effects have also been found in those of female gender (Ellenbogen *et al*. 1996) and those with family history of depression (Benkelfat *et al*. 1994) – the same groups of individuals shown to be vulnerable to depression. One possible explanation is that such individuals are genetically vulnerable to experiencing the changes that occur in depression. They may, for example, have abnormal 5-HT systems (i.e. the 5-HTT polymorphism; Caspi *et al*. 2003) or personality traits associated with negative mood. As such, they may likely to experience the depression-associated changes more readily and may, therefore, have already acquired (or partially acquired) associations during prior stress. In other words, perhaps increased vulnerability reflects an increased ease of association formation. It could, however, also be argued that vulnerable individuals who experience low mood (without having suffered an episode) negate the need for acquired associations. Such a possibility, nevertheless, seems unlikely since the ATD-induced mood effects are only of *clinical significance* in recovered depressed individuals (Ellenbogen *et al*. 1996; Booij *et al*. 2002) and it would also not explain why symptom severity appears to increase across episodes.

Limitations

The theory as presented here is based upon 5-HT and negative mood and only touches on other depression-based changes. It is likely, however, that different symptoms are not independent to begin with. Negative mood, for instance, can induce cognitive change in healthy subjects (Phillips *et al*. 2002). It is also possible that the theory is applicable only to a subset of 5-HT-related depression. Whilst similar associations could be found in other subtypes of depression, discussion of them is beyond the scope of the current editorial review.

Research also suggests that it is only remitted patients who are treated with selective serotonin re-uptake inhibitors (SSRIs) that show ATD-induced mood, patients treated with cognitive behavioural therapy (CBT) may not (O'Reardon *et al*. 2004). This could, however, be consistent with the hypothesis if one considers that CBT provides patients with top-down cognitive control over their depressive symptoms. Patients are provided with tools to counteract negative mood whenever it occurs. SSRIs, on the other hand, only increase extracellular 5-HT after an episode has taken place and so, even if SSRIs improve symptoms, they will not counteract any associations. This may also explain, in part, the delay in mood improvement following SSRI treatment.

Conclusion

MDD is often a long-term disorder. Recurrent episodes become increasingly debilitating and subsequent episodes become progressively more likely. Understanding the basis of this will hopefully lead to more effective treatments for preventing recurrence, rather than simply targeting the individual symptoms. Work is currently under way to test the hypothesis outlined here but our initial aim is to stimulate debate on the neural basis of recurrence.

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Declaration of Interest

None.

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