



Review

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'It's the way that you look at it'—a cognitive neuropsychological account of SSRI action in depression

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The fact that selective serotonin reuptake inhibitors (SSRIs) have antidepressant effects in some patients supports the notion that serotonin plays a role in the mode of action of antidepressant drugs. However, neither the way in which serotonin may alleviate depressed mood nor the reason why several weeks needs to elapse before the full antidepressant effect of treatment is expressed is known. Here, we propose a neuropsychological theory of SSRI antidepressant action based on the ability of SSRIs to produce positive biases in the processing of emotional information. Both behavioural and neuroimaging studies show that SSRI administration produces positive biases in attention, appraisal and memory from the earliest stages of treatment, well before the time that clinical improvement in mood becomes apparent. We suggest that the delay in the clinical effect of SSRIs can be explained by the time needed for this positive bias in implicit emotional processing to become apparent at a subjective, conscious level. This process is likely to involve the re-learning of emotional associations in a new, more positive emotional environment. This suggests intriguing links between the effect of SSRIs to promote synaptic plasticity and neurogenesis, and their ability to remediate negative emotional biases in depressed patients.

1. Introduction

(a) Serotonergic drugs and depression

One of the cornerstones of the serotonin hypothesis of depression is the claim that drugs that potentiate serotonin neurotransmission are effective antidepressants. This was observed with older, pharmacologically non-selective agents such as the tricyclic antidepressants and the monoamine oxidase inhibitors. However, the advent of selective serotonin reuptake inhibitors (SSRIs) indicated that agents whose acute pharmacological action is essentially confined to potentiation of serotonin activity can be useful as antidepressant drugs. Of course, other drugs which lack acute actions at serotonin neurons, for example, bupropion, are also effective antidepressants. Taken together the data suggest that serotonin potentiation may be sufficient to produce a clinical antidepressant action but it is not necessary [1,2]. Similar observations have been made concerning the role of catecholamines but the focus in this presentation will be on serotonin.

(b) Serotonin dependence of SSRIs

It has become part of clinical lore that antidepressant drugs, including SSRIs, take a number of weeks to act, that is, to produce a therapeutically beneficial effect in depressed patients. We will be examining this assumption in more detail later, but at this point, it is helpful to note that the proposed delay in onset of antidepressant drug action has given rise to an enormous volume of research investigating the neuroadaptive effects of repeated antidepressant administration in both humans and animals [1,2].

This research is based on the notion that because antidepressants take several weeks to work, their antidepressant effects cannot be because of their acute

pharmacological actions which are manifest within hours of ingestion of the first dose of treatment. Hence, the acute pharmacological actions of antidepressants must trigger a cascade of other 'adaptive' neurobiological events which evolve over time, and which are responsible for the clinical therapeutic effect [1,2].

When considering the action of antidepressants, therefore, it is important to bear in mind that acute pharmacological actions such as serotonin potentiation will be complemented by other neuroadaptive changes as the course of treatment proceeds. This gives rise to the possibility that the ability of SSRIs to potentiate serotonin neurotransmission could become less important as treatment develops and by the time the patient experiences clinical benefit, acute serotonin potentiation might be playing a relatively unimportant role in this effect.

Studies using the technique of acute tryptophan depletion (ATD) have shown clearly that this view is mistaken. ATD uses a dietary manipulation to produce an acute reduction in serotonin neurotransmission by restricting availability of tryptophan for serotonin synthesis. In patients who have responded to SSRIs and remained on treatment successfully for a number of weeks, ATD produces acute depressive relapse within a couple of hours [3]. This finding suggests that continued potentiation of serotonin function is needed for the expression of the antidepressant effect of SSRIs in depressed patients. Interestingly, patients on SSRIs do not relapse when brain catecholamine function is lowered by alpha-methyl-para-tyrosine, showing specificity of this effect to serotonin [4].

Of course, other explanations can be put forward to explain the ability of ATD to cause depressive relapse in patients taking SSRIs. For example, abrupt cessation of SSRIs produces unpleasant withdrawal symptoms [5]. If ATD produces the same effect in patients taking SSRIs, SSRI withdrawal symptomatology could be mistaken for depressive relapse. On the contrary, SSRI withdrawal produces a characteristic syndrome with anxiety, emotional lability and insomnia, and a variety of physical symptoms including dizziness, light-headedness, nausea and paraesthesia [5]. Such symptoms are not reported following ATD in patients taking SSRIs [3].

It is also conceivable that administration of SSRIs produces a form of 'serotonin dependence' such that when serotonin levels are lowered in anyone taking SSRIs, the person concerned will become depressed. This proposal is hard to test experimentally. However, a small study in healthy volunteers who were given short-term treatment with SSRIs did not find that any subjects treated in this way showed abnormal mood lowering following ATD [6].

(c) Neuroadaptive effects of SSRIs

As noted previously, numerous studies have examined the neuroadaptive effects of repeated antidepressant treatment with the aim of identifying what particular neurobiological changes coincide with the time course of the clinical antidepressant effect. Over the years, several different changes have been identified and suggested to be important in the therapeutic effect of treatment. In the case of SSRIs, a popular theory posits that desensitization of serotonin autoreceptors on serotonin cell bodies and terminals is necessary before the full effects of the SSRI to increase serotonin neurotransmission can

be expressed [7]. This interesting hypothesis suggests that combination of SSRIs with autoreceptor antagonists might facilitate speed of onset of therapeutic action and perhaps also produce a better overall clinical effect [8].

More recently, attention has been directed to the effects of repeated administration of SSRIs and other antidepressants on the elaboration of neurotrophins and other cellular processes such as synaptogenesis and neurogenesis [9,10]. A key role has been posited for the neurotrophin, brain-derived neurotrophic factor (BDNF) in terms of increasing synaptic plasticity and facilitating neurogenesis. Animal models of depression are associated with decreased BDNF production, diminished neurogenesis and impaired synaptic plasticity. These effects are reversed by repeated SSRI treatment. This finding provides a cellular basis for understanding the action of antidepressants and their delayed onset of action [11].

In fact, BDNF has rather complex roles in brain function and SSRIs do not increase BDNF in all brain regions. There are also some doubts as to whether the extent of neurogenesis, which in fact appears fairly limited and restricted to a few brain areas such as the hippocampus, can really explain the effects of antidepressants to improve mood in depressed patients [12]. However, it is interesting that antidepressants might produce effects on synaptic plasticity because this mechanism has been implicated in learning and memory, and neuropsychological process of this nature is presumably important to the action of psychotherapies in depression. It is therefore intriguing that antidepressants and psychotherapies might in some ways share a common neurobiological substrate.

(d) How long do antidepressants take to work?

As noted above, it is generally believed that antidepressants take several weeks to produce an antidepressant effect. This may give rise to the impression that no clinically discernible change in mental state occurs until a number of weeks of treatment have elapsed. However, this is not the case. A meta-analysis by Taylor *et al.* [13] examined the rate of improvement on the Hamilton Depression Rating Scale for Depression (HAM-D) week by week in depressed patients randomized blindly to treatment with either SSRIs or placebo. The HAM-D is a standard clinician-rated depression scale often used in trials of drug treatment.

The meta-analysis showed that in fact, relative to placebo, improvements in depression scores in the SSRI-treated patients were clearly apparent by the end of the first week of therapy. Indeed, the improvement seen over this time was greater than in any subsequent week though the overall difference between placebo and active drug accumulated as time went by [13]. The picture therefore is of a steady linear improvement in depressive symptoms from the very start of treatment which increased over time. This suggests that, in fact, psychological improvement starts very early in the course of antidepressant drug treatment and the apparent delay in onset of action is because of its incremental nature. That is, although the improvement starts early, it takes a number of weeks before the effect is obvious to patient and clinician. There is no evidence from this analysis of a 'step change' in antidepressant effect over a number of weeks of treatment, which suggests that similar mechanisms are likely to be involved in antidepressant action from the start of treatment up until the point at which improvement becomes clinically detectable.

2. A cognitive neuropsychological account of antidepressant action

(a) Negative emotional biases in depression and anxiety

While there has been much research on the pharmacological and cellular actions of SSRIs, there has been less attention directed to how such effects act to improve the symptoms of low mood, anxiety and social dysfunction which characterize the disorders they treat. Such a translational account may benefit from considering the actions of antidepressant drugs at a systems level, specifically on the emotion-related functions of neural systems believed to play a role in anxiety and depression.

Psychological approaches to depression have emphasized the role of negative biases in information processing in the maintenance of this disorder [14]. Mood congruent biases in the recall of emotionally valenced information in incidental memory tasks and in the monitoring and classification of emotional information have been reported to occur in depression [15,16]. Depressed patients are also more likely to classify ambiguous facial expressions as negative and this tendency persists into clinical remission [17,18]. Similarly, anxiety has been associated with attentional and interpretational biases towards threat including increased initial orienting to and recognition of fearful facial expressions [19].

The translation of these negative or threat-relevant biases of perception, attention and memory into conscious thoughts, memories and actions is believed to play a key role in precipitating and maintaining depressive states [14]. Such negative cognitions are an important target for treatment in cognitive behaviour therapy for depression and anxiety. Thus, cognitive therapists are fond of quoting the Greek stoic philosopher, Epictetus, who said, 'Men are disturbed not by things, but by the view which they take of them'. Thus, cognitive therapy aims to resolve depression by helping patients consciously reframe their negative views of themselves and the world in a more balanced way [14].

(b) Antidepressants and emotional processing

There is increasing interest in the effects of antidepressants on the way the brain processes emotional information. Such effects have been assessed in healthy volunteers, participants at risk of depression or anxiety and currently depressed patients. Here, we review this literature focusing on the effects of SSRIs on emotional processing in humans and attempt to synthesize this into a coherent account of how SSRIs may act to relieve depressive disorders. Such an account can be used to supplement neuroadaptive theories of antidepressant action by showing how psychological mechanisms recruited at the start of treatment may over time produce clinical antidepressant effects.

(c) Acute effects of SSRIs on emotional processing in healthy volunteers

(i) Behavioural effects

Although the full effects of SSRI administration on serotonin function may develop over repeated treatment through auto-receptor desensitization, there is evidence that even acute treatment increases serotonin levels to some extent. This is true both in preclinical studies measuring serotonin release

with microdialysis [20] and in indirect measures in human volunteers employing, for example, the increase in salivary cortisol as an indirect index of enhanced serotonin activity [21].

In a task of emotional processing, we found that a single dose of the SSRI, citalopram (20 mg), increased the recognition of happy facial expressions [22]. In addition, citalopram increased attention to positive socially relevant stimuli in a visual probe task after a single administration [23]. These results suggest that even acute administration of SSRIs may be sufficient to increase positive emotional processing, and thereby reverse the negative biases seen in depressed patients.

Interestingly, acute SSRI administration also appears to increase threat processing in healthy volunteers. In particular, fearful face recognition and startle responses are enhanced following acute SSRI administration [22,23]. This early increase in threat processing is consistent with clinical descriptions of increased anxiety and agitation in a subgroup of patients early in SSRI treatment before anxiolytic actions are seen [24] and a similar sequence of effects with increases in anxiety followed by anxiolytic effects has been described in animal models of anxiety [25]. This is consistent with neuroadaptive changes in serotonin and other mechanisms over the course of continued SSRI treatment.

Performance in these human models of emotional processing may therefore tap into similar underlying processes as those seen clinically and could be useful in our attempts to understand the mechanisms which mediate unwanted as well as desired effects of SSRI treatment. It is noteworthy that some antidepressants apparently decrease anxiety on acute administration in this model. For example, a single dose of mirtazapine, which acts as an antagonist at both α_2 -adrenoceptors and postsynaptic serotonin_{2A/2C} receptors, decreased fear recognition and startle responses, similar to the profile seen with repeated SSRI administration [26]. These effects are consistent with the hypothesis that the anxiolytic actions of SSRIs may relate to downregulation of postsynaptic, possibly serotonin_{2C} receptors [27].

(ii) Neuroimaging effects

A number of studies have examined the effects of acute SSRI administration on emotional processing in healthy volunteers using functional magnetic resonance imaging (fMRI). The usual model of emotional processing employed has been the presentation of emotional faces based on the well-described ability of fearful faces to increase amygdala activity as judged by the blood oxygen level-dependent (BOLD) signal. Most studies have found that acute administration of SSRIs decreases the amygdala response to fear and other aversive stimuli [28–30] (figure 1). However, one study, which used a large intravenous dose of citalopram (20 mg) found the opposite, that is, an increased amygdala response to aversive emotional stimuli [31]. Interestingly, a single oral dose of the antidepressant mirtazapine (15 mg), also decreased the amygdala response to fear [32] (figure 2). It will be of interest to explore the effect of acute treatment with antidepressants on amygdala responsivity as a common mechanism of antidepressant drug action.

Apart from the study with high-dose intravenous citalopram, these neuroimaging observations of decreased amygdala responses after acute SSRI treatment support a role for serotonin in processing threat, but do not sit easily with the observed behavioural observations of increased recognition of fearful facial

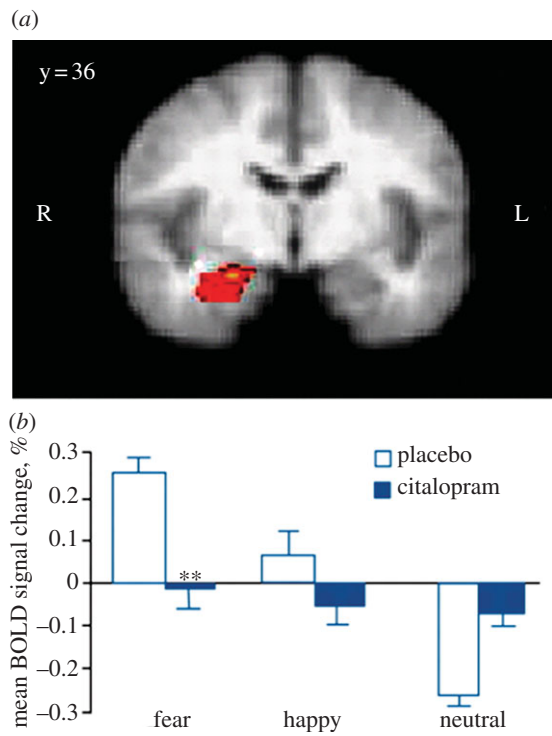


Figure 1. Effect of acute citalopram (20 mg orally) on amygdala response to emotional faces. Increased right amygdala activation in the placebo group associated with the contrast between unmasked fear and unmasked neutral faces and plot of mean percentage blood oxygen level-dependent (BOLD) signal change in this right amygdala cluster after acute oral treatment with citalopram and placebo. Image is thresholded at $Z = 2.3$, $p = 0.05$, corrected. Bars show the mean; error bars show the s.e.m. Asterisks represent significant level of difference from placebo (** $p < 0.01$). Adapted from Murphy *et al.* [30] with permission.

expressions with acute SSRI administration. It is therefore possible that the acute anxiogenic-like effects of SSRI treatment in healthy volunteers in behavioural studies do not involve the amygdala. It is also possible that if the SSRI were to increase baseline amygdala activity, there may be an apparent decrease in the response to a fearful face because a ‘ceiling’ level in amygdala response may be more easily reached. This possibility could be excluded using better characterization of baseline cerebral blood flow, with arterial spin labelling techniques in MRI.

(d) Subchronic effects of SSRI administration in healthy volunteers

(i) Behavioural effects

We have examined the effects of 7 days of treatment with SSRIs in healthy volunteers, because at this time point the effect of SSRIs to reduce ratings on clinical ratings scales of depression in depressed patients is apparent. We found further evidence of positive biasing in a number of tasks of emotional processing consistent with the effects seen after a single dose. For example, volunteers receiving 7 days’ citalopram treatment (20 mg daily) were more likely to see ambiguous facial expressions as happy and to recall positive personality adjectives in a memory task. Repeated administration of citalopram also reduced threat-relevant processing—that is, opposite to the effects of acute administration. In particular, 7 days of citalopram reduced the perception of fearful, angry and disgusted facial expressions

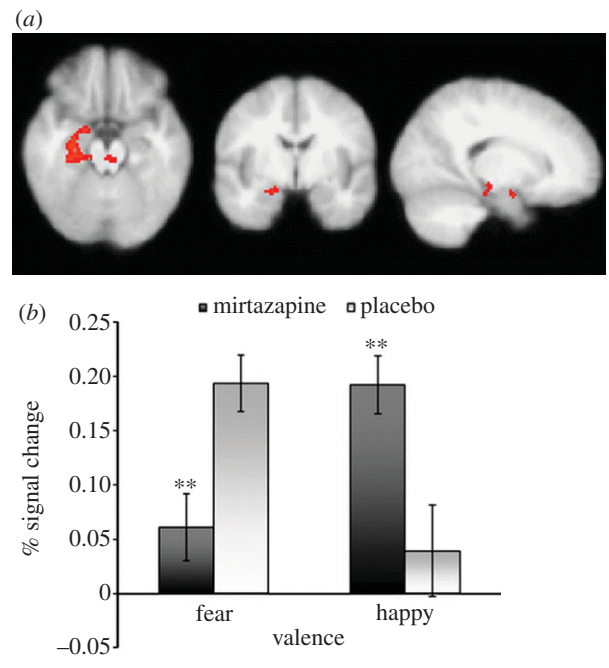


Figure 2. Effect of acute mirtazapine administration (15 mg orally) on amygdala response to emotional faces. (a) Axial, coronal and sagittal images depicting significantly increased activation in placebos for the contrast fear versus happy facial expressions (images thresholded at $Z = 2.0$, $p = 0.05$, corrected) in the right temporal cortex, extending to hippocampus and amygdala (peak voxel 28, -18 , -18). (b) BOLD percent signal change extracted from the significant cluster in the right temporal cortex to fear and happy faces. Error bars show s.e.m. ** $p < 0.01$. Adapted from Rawlings *et al.* [32] with permission.

and reduced modulation of startle responses by threat-relevant pictorial stimuli [33]. These results support the argument developed above that early increases in fear processing with acute administration may reflect initial anxiogenic actions of SSRIs which reverse with repeated treatment.

Other studies have shown that repeated SSRI administration increases affiliative problem-solving behaviour and decreases submissive behaviour in healthy volunteers [34,35], showing a striking parallel to the increased co-operation and social dominance seen with SSRI administration in male vervet monkeys [36]. Such results suggest that antidepressants not only increase the processing of positive affective stimuli but also that these effects get translated into improved social interactions and behaviour. This suggests a mechanism by which antidepressants could produce an early remediation of aspects of the social dysfunction seen in depression.

(ii) Neuroimaging

Imaging studies with fMRI show neural effects that are congruent with the behavioural changes produced by repeated SSRI administration on emotional processing. For example, our group found that 7 days of treatment of healthy volunteers with citalopram (20 mg daily) attenuated the amygdala and fusiform responses to fearful facial expressions, again a pattern opposite to the neural biases reported in depression [37] (figure 3). This finding was confirmed in healthy volunteers with either citalopram (20 mg) or escitalopram (10 mg) [38] administered in a treatment for 10 days. The apparent persistence of this effect was shown in a further study where a

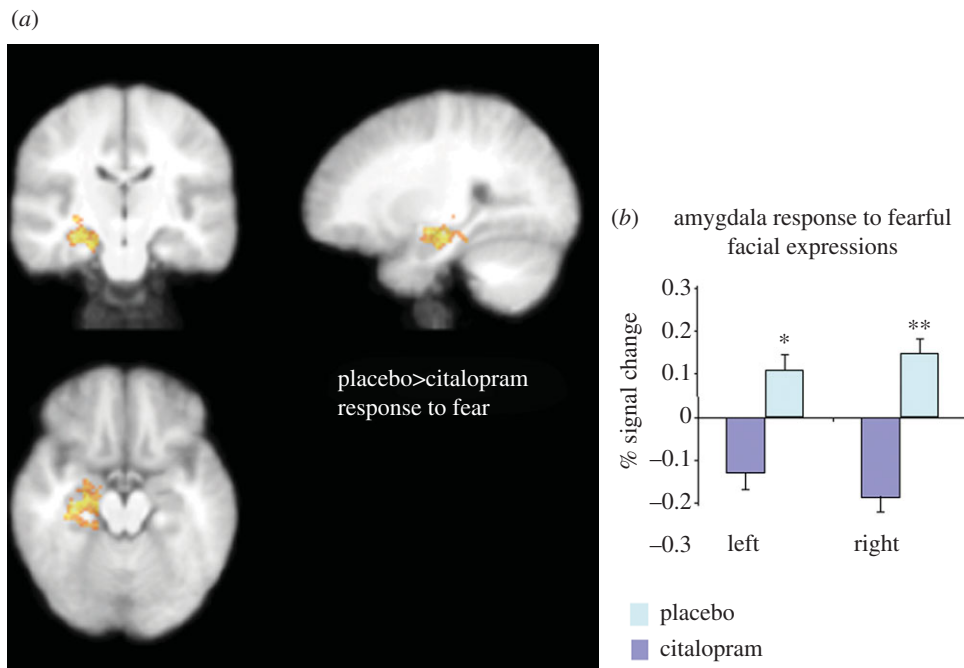


Figure 3. (a) Effect of 7 days of treatment with citalopram (20 mg daily) on the medial temporal lobe response to fearful facial expressions. Mixed effects whole-brain analysis, FMRIB Software Library (Oxford); clusters determined by $Z > 2.3$ and (corrected) cluster significance threshold of $p < 0.01$. (b) Extracted signal change from amygdala regions of interest showing decreased response to fear in both right and left sides in participants taking citalopram. Adapted from Harmer *et al.* [37] with permission.

lowered amygdala response to fear was apparent in volunteers who received escitalopram for a period of 21 days [39].

In summary, the early effects of SSRI administration on the processing of positive emotional stimuli are maintained after one week of treatment, but the effects on threat processing are reversed. This pattern of effect—increased positive bias and decreased threat-relevant bias—seems relevant to the actions of SSRI treatment in both anxiety and depression. Neuroimaging data show that the amygdala and associated visual processing circuitry (the fusiform gyrus) are modulated by SSRI drug administration suggesting a mechanism by which these drugs may affect automatic emotional evaluation of these stimuli and associated changes in attentional processing.

(e) Studies in depressed patients

Functional MRI studies of SSRI drug administration in depressed patients have yielded results largely consistent with the effects of SSRI treatment in healthy volunteer models. However, the majority of studies to date in depression have examined long-term SSRI treatment and effects of drug treatment *per se* are therefore usually confounded by resolution of depressive symptomatology.

Thus, the increased neural responses to negative facial expressions seen in the amygdala, ventral striatum and fronto-parietal cortex in depression were normalized following eight weeks of SSRI treatment, accompanied by significant improvement in mood [40,41]. This treatment also increased coupling between the amygdala and prefrontal cortex, striatum and thalamus, suggesting dynamic changes within emotional circuits important in depression [42]. Treatment with venlafaxine for eight weeks also normalized decreased anterior cingulate responses seen to negative versus neutral affective stimuli in depressed patients as well as affecting insular responses as early as two weeks after treatment [43].

Recent evidence also suggests that SSRI treatment can normalize diminished responses to positive affective stimuli in

depression, with increased extra-striate responses to happy facial expressions being seen after eight weeks of treatment and wide-spread normalization of hypoactive responses to positive affective stimuli after 22 weeks of treatment [44,45]. These findings in depressed patients suggest modulation of the same critical emotional and visual processing circuitry by SSRI treatment which is abnormal in depression.

Rather than reflecting relatively global actions of antidepressants on blood flow and related processes, these effects appear to be exquisitely modulated by stimulus valence. In particular, antidepressants appear to reduce visual and emotional processing of negative and threat-relevant emotional information while increasing the processing of positive and socially reinforcing emotional cues. While this is seen almost immediately in healthy volunteer studies, it has not been clear whether such effects are seen in neural response before mood change in depressed patients since assessments have always been carried out after at least two weeks of treatment.

In a recent study, we addressed this problem by randomizing depressed patients to either escitalopram or placebo for 7 days and examining the amygdala response to fearful faces after this period of treatment. Both placebo- and escitalopram-treated participants had very similar scores on the HAM-D at 7 days; however, the patients taking escitalopram had significant lower amygdala responses. As expected, the amygdala responses of the placebo-treated patients were significantly greater than those of healthy controls. These findings suggest that in depressed patients short-term treatment with SSRIs can indeed remediate exaggerated negative emotional biases prior to clinically significant improvement in mood.

(f) Implications for antidepressant action and the 'delayed' clinical response

The findings which we have reviewed indicate that antidepressants can produce rapid changes in the processing of emotional

information. Both acute and short-term SSRI treatment lead to positive biases in emotional perception and memory, that is, the opposite effects to those seen in the depressed state.

Although the effects of antidepressants on emotional processing appear to be present from the initiation of treatment, it is clear that time is needed before subjective improvement is substantial, although probably rather less than has traditionally been assumed. Our data suggest that antidepressants act on early and relatively automatic stages of information processing, prior to subjective improvement in clinical state. Indeed, both behavioural data from the dot-probe task and the neural loci of SSRI are consistent with a modulation of attentional processing of emotional stimuli even at very fast presentation times [23,33]. This is consistent with effects on initial orienting to these stimuli.

However, the subjective experience of depression is very much associated with conscious negative appraisal and evaluation of emotional life. How could this be altered by changes in automatic emotional processing? We suggest that the positive re-biasing of automatic processing produced by acute SSRI might, in an appropriate interpersonal environment, lead to changes in the strategic processing associated with conscious emotional experience. Such a psychological process might well involve 're-learning' a range of emotional associations which would inevitably take time and exposure to a real-world environment. On this view, antidepressant drugs have 'bottom-up' effects on emotional processing which become translated into improved mood and conscious appraisal only over time and with experience of life in the context of new processing biases.

The notion that re-learning might be involved in subjective improvement in depression sits intriguingly with the observation that antidepressants promote synaptic plasticity in animal experimental studies [11]. It is possible that antidepressants can produce effects on synaptic plasticity independent of their actions on emotional processing and that the increased synaptic plasticity facilitates the emotional re-learning process which we have hypothesized above. But, equally, increased synaptic plasticity may be facilitated by the alterations in emotional experience produced by the antidepressant, perhaps analogous to the way in which manipulations of the external environment can also promote synaptic plasticity in animal studies [46].

Depression is a complex clinical syndrome characterized not only by lowered mood but also by vegetative and

cognitive symptoms. How far can changes in emotional processing account for the resolution of this multiple symptomatology during the course of successful antidepressant treatment? We suggest that the changes in emotional processing we have described can indeed explain this kind of global improvement because attention and appraisal are of fundamental importance in how the brain decides what matters to it. Thus, the ability of antidepressant drugs to interfere with a preferential focus on negative stimuli means that the brain is once again open to emotionally positive information and positive interpretation of experience.

We have argued above that this effect, over time, could lead to greater reactivity and improvement in mood and a decrease in social and occupational withdrawal. In the same way, the lessening of preoccupation with negative themes could free up processing resources for tasks such as episodic memory which are typically impaired in the depressive state [47]. Equally, vegetative symptoms can be strongly influenced by attention and appraisal. For example, fluvoxamine treatment in depressed patients was associated with improvement in reported subjective sleep quality even though objectively measured sleep parameters showed a trend to worsen [48]. Of course, negative biases in information processing have long been a target of cognitive behavioural therapy for depression, and it is therefore of interest that antidepressant drugs may also act on similar emotional mechanisms but presumably at an implicit rather than explicit level.

If this hypothesis is correct one might expect that the early changes in emotional bias produced by antidepressant treatment would predict eventual therapeutic outcome and this proposal is supported by some preliminary evidence, which requires replication and extension [49]. It is also of great interest that negative biases in emotional processing may be persistent in recovered unmedicated patients who demonstrate abnormalities in behavioural and neural responses similar to those apparent in acute depression [50,51]. It would be predicted that such biases should be attenuated by continued antidepressant treatment. This may provide a mechanism for the established efficacy of antidepressant treatment in long-term maintenance therapy and a possible means of identifying patients who require it.

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