Manipulating serotonin function in depression

Merens, W.

8

The effects of serotonin manipulations on emotional information processing and mood

W. Merens, A. J. W. Van der Does, P. Spinhoven. (2007).
Journal of Affective Disorders, 103, 43-62

Abstract

Serotonin is implicated in both mood and cognition. It has recently been shown that antidepressant treatment has immediate effects on emotional information processing, which is much faster than any clinically significant effects. This review aims to investigate whether the effects on emotional information processing are reliable, and whether these effects are related to eventual clinical outcome. Treatment-efficiency may be greatly improved if early changes in emotional information processing are found to predict clinical outcome following antidepressant treatment. This is a review of studies investigating the short-term effects of serotonin manipulations (including medication) on the processing of emotional information, using PubMed and PsycInfo databases. Twenty-five studies were identified. Serotonin manipulations were found to affect attentional bias, facial emotion recognition, emotional memory, dysfunctional attitudes and decision making. The sequential link between changes in emotional processing and mood remains to be further investigated. The number of studies on serotonin manipulations and emotional information processing in currently depressed subjects is small. No studies yet have directly tested the link between emotional information processing and clinical outcome during the course of antidepressant treatment. Serotonin function is related to several aspects of emotional information processing, but it is unknown whether these changes predict or have any relationship with clinical outcome. Suggestions for future research are provided.

Introduction

Major depressive disorder is one of the most disabling diseases in the world (Üstün et al., 2004). Of the people who have been treated for a depressive episode, 50% will get depressed again. This percentage increases to a 90% chance of a future depression, having experienced three depressive episodes in the past (Judd, 1997). The most effective treatments for depression are antidepressant medication, structured forms of psychotherapy (eg. cognitive behavioural therapy), or a combination. Selective serotonin reuptake inhibitors (SSRIs) form the most widely used pharmacological treatment for depression (Petersen et al., 2002). The monoamine theory of depression states that monoamine levels, such as serotonin, are low in the brain during untreated depressive episodes, but no explanation had been found for how monoamine loss occurs (Maes & Meltzer, 1995). Recently, Meyer et al. (2006) found evidence that elevated monoamine oxidase (MAO-A) density may be the primary monoamine-lowering process during depression.

Serotonergic antidepressants increase brain serotonin function by inhibiting the re-uptake of the neurotransmitter serotonin (5- hydroxy-triptamine; 5-HT) (Blier & de Montigny, 1994). Research has indicated that 80% occupancy of the serotonin transporter (5-HTT) may be necessary for the therapeutic effect of SSRIs to occur (Meyer et al., 2004). One puzzling factor in the treatment with SSRIs is the delay in onset of action. A recent meta-analysis (Taylor et al., 2006) suggests that treatment with SSRIs may lead to clinical improvement as early as the end of the first week. Although this is faster than is commonly assumed, there is still a considerable delay between the biochemical effects of SSRI administration and symptomatic improvement. One possible explanation for this delay in onset is a process called 'receptor desensitization'. All SSRIs enhance the activity of the 5-HT1a autoreceptor via

the blockade of the 5-HT transporter in the raphe nuclei (Blier & de Montigny, 1998). After two to three weeks, 5-HT transmission is increased in the brain because of a normalized firing rate in the presence of sustained 5-HT reuptake blockade and because the terminal 5-HT autoreceptor is desensitised. The autoreceptors normally have an inhibitory effect on the amount of serotonin that is released per impulse. After long-term administration of an SSRI, this inhibitory effect is lifted (Blier & de Montigny, 1998).

Evidence for this receptor desensitisation-hypothesis comes from studies investigating the effects of the 5-HT1a/β-adrenoreceptor antagonist pindolol in combination with SSRI treatment. Pindolol blocks the 5-HT1a autoreceptor on the cell body of 5-HT neurons to prevent the initial decrease in firing activity of these neurons at the start of SSRI treatment. This process mimics the desensitisation of the 5-HT1a autoreceptor, which occurs after about 2 weeks of SSRI treatment. Pindolol has been found to accelerate the therapeutic effect of SSRIs (Ballesteros & Callado, 2004; Perez et al., 1997) although results have been conflicting (Berman et al., 1997; Moreno et al., 1997).

Cognitive effects of antidepressant treatment

A recently proposed alternative explanation for the delay in therapeutic response following treatment with antidepressants is that cognitive changes, which may occur within hours after administration, mediate the antidepressant response (Amado-Boccara et al., 1995; Harmer et al., 2003b). Very brief (one day or one week) treatment with a serotonergic antidepressant caused selective changes in emotional information processing, in particular changes in the recognition of facial expressions of emotions (Bhagwagar et al., 2004; Harmer et al., 2004). It may take a number of days or weeks for these changes to build

up to a clinical (mood) effect (Harmer et al., 2003a). This hypothesis receives indirect support from research showing that experimental lowering of serotonin may also lead to cognitive changes in the absence of changes in mood (Hayward et al., 2005; Murphy et al., 2002; Park et al., 1994).

In the psychological treatment of depression the emphasis lies on reducing negative cognitions and information processing biases. The research on the immediate cognitive effects of antidepressant treatment suggests that similar effects may occur in pharmacotherapy (Harmer et al., 2003b). This idea remains speculative but is the basis for recent studies on the acute cognitive effects of antidepressants and hypotheses about their relation to a clinical response (Bhagwagar et al., 2004; Harmer et al., 2002; Harmer et al., 2003a; Harmer et al., 2003b). To test this idea, cognitive functions should be measured in patients before starting on an SSRI and for the first few weeks of treatment, to investigate whether any changes in emotional information processing are related to subsequent mood response. If clinical outcome can be predicted on the basis of short-term changes in emotional processing, earlier switching to another antidepressant may become feasible. However, such a study seems premature considering how little is known of the relation between cognitive and mood effects following SSRI treatment.

SSRIs may regulate emotional information processing by activating plasticity processes via brain-derived neuroptrophic factor (BDNF) in neural networks associated with mood regulation. Serum BDNF is suggested to influence plasticity. Structural alterations in neuronal plasticity occur in patients with mood disorders (Sheline et al., 1999). Supporting this notion are findings that indicate baseline levels of serum BDNF in depressed patients were significantly lower than those of controls (Gonul et al., 2005). However, after eight weeks of SSRI treatment serum BDNF levels had increased significantly

and differed no longer from those of controls. The exact timeline of the changes in BDNF is of yet unknown but seems to resemble that of clinical response and may thus be slower than the process of receptor desensitisation. Also a post-mortem study found increased BDNF expression in hippocampal regions at the time of death in patients treated with antidepressants compared to untreated patients (Chen et al., 2001). It was therefore concluded that antidepressants may normalize hippocampal levels of this important neuroprotective factor. Animal studies showed that chronic stress and chronic antidepressant treatment are associated with long-lasting changes in BDNF gene expression in the hippocampus (Tsankova et al., 2006). Since the hippocampus contributes to altered mood in depression and to cognitive function (Duman, 2004), a possible link between SSRIs, emotional processing and plasticity is suggested.

The aim of the present paper is to review the available evidence concerning the hypothesis that cognitive changes mediate the effects of antidepressant treatment. This hypothesis is based on three assumptions. The first assumption is that serotonin manipulations (in particular the administration of antidepressants) have reliable effects on emotional information processing. The second is that these effects are also observed in currently depressed patients starting antidepressant treatment. The third assumption is that the cognitive effects of antidepressants predict clinical outcome. No studies have yet addressed the third assumption. We will therefore focus our review on the first two assumptions, and summarize the studies that measured short-term effects of serotonin manipulations on emotional information processing and mood and the effects of pharmacotherapy on emotional information processing and mood in depression. We will first briefly summarize the cognitive dysfunctions that are

associated with depression, which is necessary to assess whether any cognitive changes induced by serotonin manipulations are clinically relevant. In addition, different aspects of emotional information processing related to depression will be discussed.

Neutral and emotional information processing in depression

Cognitive dysfunctions (eg. dysfunctions in the processing of neutral as opposed to emotional information) associated with depressive disorders have been subject of many studies (Deuschle et al., 2004; Elliott, 1998; Paradiso et al., 1997). Clear conclusions on the exact cognitive dysfunctions are difficult to draw because of the large differences among studies in subject samples, methods and design. Also, most tests are linked to a number of different cognitive domains, making it difficult to clarify the primary deficit when performance is impaired (Austin et al., 2001). Cognitive dysfunctions that are often impaired in depression include memory, learning, attentional set-shifting, psychomotor speed, sustained attention, and complex problem solving (Austin et al., 2001; Weiland-Fiedler et al., 2004). Effortful executive tasks, which are related to the functioning of the prefrontal cortex, are most often impaired (Elliott, 1998). Cognitive impairments are also found in recovered depressed patients; however these effects are usually statistically non-significant after controlling for residual depressive symptoms, except for attentional deficits (Paelecke-Habermann et al., 2005; Weiland-Fiedler et al., 2004).

Apart from dysfunctions in the processing of neutral information, dysfunctions in emotional information processing have also been studied extensively. The earliest studies investigated a mood-congruent memory bias: depressed patients have a better memory for disorder-related information

(Blaney, 1986; Bower, 1981; Teasdale, 1983), and impaired memory for positive information (Matt et al., 1992).

Depressed patients also have difficulties in retrieving *specific* autobiographical memories (Brittlebank et al., 1993; Kuyken & Dalgleish, 1995; Williams & Scott, 1988). This deficit may even persist into the euthymic phase (Peeters et al., 2002) and predicts depressed mood after a stressful life event (Van Minnen et al., 2005).

Compared to healthy volunteers, depressed patients are impaired in the recognition of facial expressions of emotions. Both a general deficit in the recognition of emotions as well as emotion-specific impairments have been found (Bouhuys et al., 1999; Gur et al., 1992; Persad & Polivy, 1993; Rubinow & Post, 1992). A recent study showed subtle impairments in discrimination accuracy as well as a bias away from the identification of happy faces (Surguladze et al., 2004).

Murphy et al. (2001) investigated decision making in manic and depressed patients and healthy controls using a gambling task. Both patient groups showed delayed deliberation times and altered betting strategies, however only the manic patients were impaired in the quality of their decisions. In the depressed and the control group, the subjects who were slowest were also the ones that made suboptimal decisions.

Depressed patients have been found to show an attentional bias for negative stimuli. This bias is thought to be not only a symptom of depression, but also to be important in the development and maintenance of depressive disorders (Williams et al., 1996). The literature on attentional bias in depression is contradictory, which may be explained by the fact that different measures of attentional bias (e.g. the Stroop and the dot-probe test) are not necessarily inter-correlated and may even assess different constructs (Gotlib et al., 2004).

Higher-order cognitive processes in depression are also distorted: depressed patients hold negative schemas about oneself, the world and the future (Beck, 1976). These dysfunctional cognitions can be assessed with the Dysfunctional Attitudes Scale (DAS) (Beck, 1976; Weissman, 1979). In acutely depressed patients, DAS scores are significantly increased compared to healthy controls; however they normalize following clinical recovery. When negative mood increases, the level of dysfunctional attitudes has been found to increase more in recovered depressed patients than in healthy controls (Ingram et al., 1998). This increase in DAS scores in response to relatively small deteriorations of mood has been labelled cognitive reactivity (CR). Higher CR scores have been associated with an increased risk of relapse in recovered depressed subjects (Segal et al., 2006).

Overall, depressed patients show impairments in several cognitive domains, such as memory, learning, attentional set-shifting, psychomotor speed, sustained attention, planning, inhibitory control and problem solving. Impairments in emotional information processing include the recognition of facial expressions of emotions, attentional bias toward negative material, an over-general autobiographical memory, an increased level of dysfunctional attitudes and impaired decision making. Only some of these impairments are detectable in remitted depressed patients.

As noted above, the framework of this review is the hypothesis that cognitive changes mediate the antidepressant response. Because of a lack of studies directly testing this hypothesis, we will review studies 1) on the short-term effects of serotonin manipulations on emotional information processing and mood in healthy and depression-vulnerable individuals and depressed

patients, and 2) on the changes in emotional information processing and mood in depressed patients starting antidepressant treatment.

Methods

A literature search was performed with PubMed and PsycInfo databases (1966-2006) using the following key words: serotonin, depression, emotional information processing, cognition, SSRI, and tryptophan. We also searched reference lists of papers that seemed suitable to review. Twenty-five studies were identified through this combined search strategy to be eligible for inclusion in this review. The first study was published in 1994 and the most recent studies were published in 2006. Studies were divided into four classes on the basis of the manipulation that was used:

- four studies on short-term effects of administration of a serotonergic antidepressant (SSRI)
- two studies using a serotonin-receptor agonist or antagonist
- three studies using dietary manipulations (e.g. tryptophan loading)
- sixteen studies using acute tryptophan depletion (ATD)

Results

All studies including their subject sample, methods, outcome measures and results are shown in Table 1.

Table 1. Effects of serotonin manipulations on emotional information processing and mood

Authors	Sample	Intervention	Outcome measures	Results
SSRI studies				
Harmer et al. (2003a)	*n* = 25 healthy women	Citalopram (10 mg) vs. saline (5 ml); single, intravenous administration	- Facial expression recognition task - VAS scales, BFS	A better and faster recognition of fear and happiness was found after citalopram. No effects on mood were found.
Bhagwagar et al. (2004)	*n* = 20 unmedicated euthymic women with a history of MDD n = 20 healthy women	Citalopram (10 mg) vs. saline; single, intravenous administration	- Facial expression recognition task - VAS scales	Citalopram decreased recognition of fear in recovered depressed subjects and increased fear recognition in healthy subjects; citalopram increased subjective anxiety more in recovered depressed women.
Harmer et al. (2004)	*n* = 42 healthy volunteers	Citalopram (20 mg/day) vs. reboxetine (8 mg/day) vs. placebo; 7 days, oral administration	- Facial expression recognition task - Emotional categorization task - Emotional memory - Emotion potentiated startle - STAI, BDHI, BDI, PANAS, SASES, BFS	Citalopram and reboxetine reduced recognition of anger and fear and increased recall of positive material. Citalopram abolished the emotional startle response to negative stimuli. Reboxetine decreased subjective feelings of hostility and increased energy.

Table 1. (*continued)*

Authors	Sample	Intervention	Outcome measures	Results
Harmer et al. (2006a)	*n* = 24 healthy volunteers	citalopram (20 mg/day) vs. placebo; 7 days, oral administration	- Masked facial expression recognition task - Facial expression recognition task - STAI, BDHI, BDI, BFS, VAS scales	Citalopram attenuated the neural response to fear, decreased the recognition of fearful facial expressions and reduced subjective hostility.
5-HT receptor agonist / antagonist studies				
Meyer et al. (2003)	1) *n* = 29 healthy volunteers	d-fenfluramine (0.3 mg/kg) vs. clonidine (1.4 μg/kg) ; single intravenous administration	- Dysfunctional attitudes scale - VAS scales	DAS scores decreased after administration of d-fenfluramine compared to placebo.
	2) *n* = 22 unmedicated depressed subjects; *n* = 18 subjects with a history of self-harm; *n* = 29 healthy volunteers		- Dysfunctional attitudes scale - cortex 5-HT2 receptor binding potential using [18F]setoperone PET - HAM-D	Depressed subjects with high DAS scores had higher 5-HT_2 BP compared to healthy subjects.
Harmer et al. (2006b)	*n* = 24 healthy volunteers	Ondansetron (12 mg) vs. lactose; single, oral administration	- Facial expression recognition task - Emotional categorization task - Emotional memory - Emotion potentiated startle - STAI, VAS scales	Ondansetron diminished the emotion potentiated startle. No effects were found on mood, facial expression recognition or emotional memory.

Table 1. *(continued)*

Authors	Sample	Intervention	Outcome measures	Authors
Tryptophan augmentation studies				
Luciana et al. (2001)	*n* = 19 healthy volunteers	Tryptophan loading (single administration) vs. ATD	- Digit span/ spatial span[a] - Letter cancellation task - Spatial working memory - Affective working memory - Verbal fluency - Finger tapping test - Grooved pegboard test - PANAS	Both tryptophan loading and ATD decreased positive affect. ATD increased motor performance. Tryptophan decreased motor coordination and verbal and affective working memory (only negative content) and increased immediate attention.
Murphy et al. (2006)	*n* = 38 healthy volunteers	Tryptophan (1 g 3x/day) vs. placebo; 14 days, oral administration	- Facial expression recognition task - Emotion potentiated startle - Attentional probe task - Emotional categorization - Emotional memory - Dysfunctional attitudes scale - PANAS, STAI, BDHI, BDI, BFS	Tryptophan increased the recognition of happiness, decreased the recognition of disgust in females, reduced attentional vigilance to negative words and decreased baseline emotional startle response. No effects on mood or dysfunctional attitudes were found.

Table 1. *(continued)*

Authors	Sample	Intervention	Outcome measures
ATD studies			
Park et al. (1994)	*n* = 12 healthy men	ATD vs. placebo	- Spatial working memory test - Tower of London - Visual discrimination test (attentional set shifting) - Paired associated learning - Pattern and spatial recognition test - Rapid visual information processing - Autobiographical memory test - VAS scales	ATD selectively impaired learning and retrieval. No effects on mood were found.
Coull et al. (1995)	*n* = 12 healthy volunteers	ATD vs. placebo[b]	- Emotional selective attention task	ATD reduced reaction times to incompatible stimuli, but not to compatible stimuli. (independent of emotional valence). No effects on focused attention were found.
Rogers et al. (1999a)	*n* = 31 healthy volunteers[c]	ATD vs. placebo	- Decision making task	ATD impaired decision making: the tendency to choose the least probable outcome and deliberation times were increased.

Table 1 *(continued)*

Authors	Sample	Intervention	Outcome measures	Results
Rubinsztein et al. (2001)	*n* = 30 healthy volunteers	ATD vs. placebo	- Affective go/no-go task - Visual pattern recognition task - POMS, VAS scales	ATD impaired 'maintenance of set' and visual delayed recognition. No effect on mood was found.
Klaassen et al. (2002)	*n* = 16 healthy volunteers (FH+)[1] *n* = 11 healthy volunteers (FH-)	ATD vs. placebo	- Visual verbal learning test (positive and neutral words) - POMS	ATD lowered mood in FH+ subjects and impaired delayed recall of neutral and positive words but not negative words in all subjects.
Murphy et al. (2002)	*n* = 12 healthy women	ATD vs. placebo	- Probability reversal task - Affective go/no-go task - Tower of London - HAM-D, VAS scales	ATD slowed the processing of happy material and slowed responding in a visual discrimination and reversal learning task. No effects on planning or mood were found.
Anderson et al. (2003)	*n* = 28 healthy volunteers	ATD vs. placebo	- Gambling task	No effect of ATD on probabilistic choice was found.
Harmer et al. (2003c)	*n* = 38 healthy volunteers	ATD vs. placebo	- Facial expression recognition task - PANAS	ATD impaired recognition of fear only in women. No effects on reaction times or mood were found.

Table 1. *(continued)*

Authors	Sample	Intervention	Outcome measures	Results
Rogers et al. (2003)	*n* = 18 healthy volunteers	ATD vs. placebo	- Decision making task	ATD impaired decision making.
Booij et al (2005c)	*n* = 20 medicated remitted depressed patients	High-dose vs. low-dose ATD	- Self-referent adjectives encoding and recall task - MADRS, BAS, CPRS, BDI-II, PANAS	High-dose ATD decreased the consistency of positive trait ratings and decreased immediate recall of positive words in mood-responders.
Booij et al. (2005a)	*n* = 20 medicated remitted depressed patients	High-dose vs. low-dose ATD	- Tower of London - Stroop task (neutral and emotional) - Abstract patterns recognition task - Letter fluency - Left/right choice reaction time - MADRS	High-dose ATD impaired the processing of positive information, independent of mood change. ATD improved attention for neutral information in a dose-dependent manner. High-dose ATD increased depressive symptoms in a subgroup of patients.
Evers et al. (2005)	*n* = 15 healthy volunteers	ATD vs. placebo	- Probabilistic reversal learning task - Visual verbal learning test (positive and neutral words) - Abstract pattern learning task - VAS version of POMS	ATD increased reaction times for delayed recognition on verbal learning. No effects on mood were found.

Table 1. *(continued)*

Authors	Sample	Intervention	Outcome measures	Results
Hayward et al. (2005)	*n* = 24 unmedicated recovered depressed patients *n* = 24 healthy volunteers	Low-dose ATD vs. placebo	- Stroop task (neutral and emotional) - Emotional memory task - Auditory verbal learning task - Emotion potentiated startle - Facial expression recognition task - BDI, POMS, VAS scales, HAM-D	Low-dose ATD did not affect mood. ATD produced an elevation of the startle response, impaired recognition of happiness, impaired initial recall memory and increased emotional interference in the recovered depressed group. In healthy subjects, ATD enhanced recognition of happiness and increased emotional interference.
Talbot et al. (2006)	*n* = 32 healthy volunteers	ATD vs. placebo	- Decision making task - ID/ED attentional set-shifting task - VAS scale	ATD improved decision-making. No effects on risk taking, speed of decision making, set-shifting, reversal learning or mood were found.
Evers et al. (2006)	*n* = 15 healthy women	ATD vs. placebo	- Stroop task (neutral and emotional) - POMS	ATD increased interference for negative words and decreased interference on the neutral Stroop. No effect on mood was found.

Table 1. *(continued)*

Authors	Sample	Intervention	Outcome measures	Results
Munafò et al. (2006)	*n* = 24 medicated recovered depressed patients *n* = 24 unmedicated recovered depressed patients *n* = 24 healthy volunteers	Low-dose ATD vs. placebo	- Stroop task (emotional) - BDI, POMS, VAS scales, HAM-D	ATD increased the processing of social threat cues and self-rated depression only in medicated recovered depressed patients.

BAS = Brief Anxiety Scale, BDI = Beck Depression Inventory, BDHI = Buss-Durkee Hostility Inventory, BFS = Befindlichkeits Scale, CPRS= Comprehensive Psychopathological Rating Scale, HAM-D = Hamilton Rating Scale for Depression, MADRS = Montgomery-Asberg Rating Scale for Depression, MDD = Major Depressive Disorder, PANAS = Positive and Negative Affect Scale, POMS = Profile of Mood States, SASES = Social Adaption Self Evaluation Scale, STAI = State-Trait Anxiety Inventory, VAS = Visual analogue scale, [1] FH = Family history of major affective disorder,
[a] Neuroendocrine measures were also taken but are not reported here, [b] The effects of clonidine, diazepam and haloperidol were also studied but are not reported here, [c] Amphetamine users, opiate users, frontal subjects and ORB-PFC patients were also included but these results are not reported here.

Selective serotonin reuptake inhibitor studies

It has long been known that antidepressant medications have effects on cognitive function. For instance, a review by Thompson (1991) shows a wide range of effects of antidepressants on memory. The effects varied from improvement to no effect to impairment, and there was limited evidence for specific effects of different antidepressants. In patients with memory impairments, SSRIs possibly had a positive effect on memory (Thompson, 1991). Amado-Boccara et al. (1995) also reviewed the effects of antidepressants on –neutral- cognitive performance. They concluded that serotonergic antidepressants either had no effect on reaction time tasks and psychomotor functioning or caused small improvements. The authors noted that the acute effects differed from the effects on the middle and long- term. For most antidepressants a tolerance effect occurs after a week or two. In depressed individuals who often suffer from impairments in memory and concentration, a normalization of cognitive function accompanies mood improvement following long-term administration of an SSRI.

More recent research has focused on the acute effects of SSRIs on the processing of emotional, in contrast to neutral, information (Bhagwagar et al., 2004; Harmer et al., 2003a). This seems to yield more consistent findings. Harmer et al. (2003a) investigated the effects of intravenous administration (over 30 minutes) of 10 mg citalopram or saline (placebo) on mood and information processing in healthy women. Participants completed the assessments 30 minutes after the end of the infusion. Compared to placebo, participants were better and faster at recognizing facial expressions of happiness following citalopram. Contrary to expectation, the recognition of fearful facial expressions also improved. No immediate effects of citalopram on mood were observed. Bhagwagar et al. (2004) compared the effects of

citalopram on facial expression recognition in women with and without a history of depressive episodes. A single dose of citalopram or placebo was administered intravenously and effects were measured 30 minutes after the infusion. The women with a history of depression showed a better recognition of fear at baseline compared to healthy women, which was normalized following administration of citalopram. This effect was opposite to the effect seen in the healthy women, in whom the recognition of fear increased following citalopram. Subjective anxiety levels were increased after citalopram in both groups, although this effect tended to be stronger in the participants with a history of depression. These results suggest that a negative cognitive bias may persist into the euthymic phase and that this cognitive vulnerability is sensitive to antidepressant administration. The authors suggested that the effect of the antidepressant on the processing of fear (increasing vs. decreasing) may be dependent on baseline levels of fear processing. This however was not tested and no other studies have reported baseline levels of facial emotion recognition to be of influence on the response to serotonergic modulation.

Harmer et al. (2003a) suggest that changes in the processing of emotional information may occur independently of changes in mood. Also, there appear to be significant differences between the acute effects of SSRI administration and the effects of repeated ('sub-chronic') SSRI administration. A seven-day administration of citalopram (20 mg/day) or the selective norepinephrine reuptake inhibitor (SNRI) reboxetine (8 mg/day) in healthy volunteers resulted in a decreased recognition of anger and fear, and an increased memory for positive material (Harmer et al., 2004). Citalopram also abolished the increased startle response to negative stimuli. Mood and anxiety were not significantly affected. Another study also found decreased recognition

of fear after a seven-day administration of citalopram (20 mg/day) compared to placebo, which was accomplished by a reduced neural response to fear measured by functional Magnetic Resonance Imaging (fMRI). Citalopram also reduced subjective hostility (Harmer et al., 2006a). A single dose of an SSRI however resulted in increased levels of fear recognition in healthy subjects (Harmer et al., 2003a). These effects of SSRIs on the processing of fearful facial expressions are mirrored in the initial increase of symptoms of anxiety during the early phase of SSRI treatment before these and other symptoms eventually decrease (Bagdy et al., 2001; Humble & Wistedt, 1992). However, a single dose of an SSRI not only increased fear recognition but also the recognition of happiness (Harmer et al., 2003a). This might indicate that serotonin manipulations have a general effect on perception rather than a specific effect on the recognition of certain –positive or negative- emotions. The fact that serotonin affects a positive and negative emotion in the same direction, may also indicate that there are two separate processes. On the one hand an effect of SSRIs on fear recognition, which reverses from acute to repeated administration. On the other hand there is a positive effect of SSRIs on affective processing (i.e. on the recognition of happy facial expressions, emotional memory and attentional bias) which is seen very early with antidepressant drug administration and is still observed after 1 week of treatment. It remains to be seen which of these effects is related to clinical improvement, if any.

Conclusion

Short-term administration of an SSRI increases the processing of fear and happiness in healthy individuals and decreases the processing of fear in recovered depressed women. Sub-chronic administration of an SSRI in healthy

subjects results in opposite effects compared to acute administration, e.g. a decreased recognition of anger and fear. Mood is affected by SSRI administration but only in recovered depressed patients and independent of emotional information processing.

Serotonin receptor agonist / antagonist studies

Challenge procedures using 5-HT receptor agonists and antagonists have been widely used. Apart from neuro-endocrine effects, cognitive effects have also been investigated, but rarely. Riedel et al. (2002) found that the 5-HT_{2c} agonist metachlorophenylpiperazine (m-CPP), but not the 5-HT_{1a} agonist ipsapirone selectively increased depression and tension in depressed patients. Ipsapirone however impaired immediate recall in controls but improved immediate recall in depressed patients. m-CPP impaired signal detection efficiency in controls but not in patients in a visual search task and impaired reaction times in both groups on a choice reaction time task. These results support the hypothesis that depression is associated with 5-HT_{1a} receptor desensitisation and 5-HT_{2c} receptor sensitisation.

Meyer et al. (2003) investigated the effects of *d*-fenfluramine vs. clonidine (an α_2 receptor agonist, as a placebo) on dysfunctional attitudes (measured with the DAS) and 5-HT_2 receptor binding potential (BP) in the cortex. Three different groups were studied: unmedicated depressed patients, patients with a history of self-injurious behaviour outside of a depressive episode (all with an Axis II diagnosis of Borderline Personality Disorder) and healthy controls. The rationale for this study was based on the finding that suicide victims with and without major depressive episodes have elevated levels of 5-HT_2 receptor density in the prefrontal cortex (Arango et al., 1990; Hrdina et al., 1993). Since higher levels of dysfunctional attitudes are found in

depressed patients with and without suicidal tendencies, the authors hypothesized that 5-HT_2 BP and dysfunctional attitudes may be related. Results showed that dysfunctional attitudes improved significantly more after *d*-fenfluramine compared to clonidine in healthy subjects. No effects on subjective mood were found. In a second experiment, dysfunctional attitudes were found to be strongly related to 5-HT_2 BP in all cortex brain regions in depressed patients. This was not true for patients with a history of self-harm and healthy controls. A subgroup of depressed patients with high DAS scores had greater 5-HT_2 BP in all investigated brain regions compared to healthy controls. These results indicate a relationship between serotonin and the level of dysfunctional attitudes. Also, depressed patients with high levels of dysfunctional attitudes showed low levels of 5-HT agonism and higher 5-HT_2 BP compared to healthy subjects. In the patients with self-injurious behaviour, cortex 5-HT_2 BP was unrelated to the levels of dysfunctional attitudes. The authors concluded that a deregulated neuromodulation of serotonin seems to play an important role in the pathophysiology of dysfunctional attitudes. This might indicate that SSRI-treatment affects the same cognitive processes which are also the focus of cognitive therapy. Simons et al. (1984) have found that antidepressant therapy and cognitive therapy resulted in similar changes on various measures, including dysfunctional attitudes. Again, the results of this study suggest that cognitive processes are sensitive to changes in serotonin function. Recently, more evidence was found to support the link between 5-HT receptor BP and dysfunctional attitudes (Bhagwagar et al., 2006). Recovered depressed patients demonstrated elevated cortical 5-HT_{2A} receptor BP compared to healthy volunteers and 5-HT_{2A} BP correlated positively with DAS scores only in recovered depressed patients. However, future research is needed since no other studies have looked at the acute reactivity of

dysfunctional attitudes following manipulations of serotonin function, e.g. soon after initiating SSRI treatment. Also, the link between 5-HT_2 BP and dysfunctional attitudes was only significant in a small subgroup of depressed patients (those with a high level of dysfunctional attitudes). No link between cortex 5-HT_2 BP and DAS scores in patients with chronic self-harm behaviour was found. The authors suggested that the extreme psychological factors playing a role in borderline personality disorder may obscure the relationship between dysfunctional attitudes and serotonin. Also, other serotonin abnormalities that do not influence 5-HT_2 BP may play a role.

One study investigated the effects of a serotonin receptor antagonist on emotional processing (Harmer et al., 2006b). Healthy volunteers were given either 12 mg ondansetron (a $5HT_3$ antagonist) or placebo orally. The effects on facial emotion recognition, emotional categorization and memory and emotion potentiated startle were assessed as well as mood. Results indicated that ondanstron reduced the emotion potentiated startle, especially in response to negative pictures. Contrary to the effects of acute SSRI administration, no effects were found on facial emotion recognition. Also no effects were found of ondansetron on mood or emotional memory. These results suggest a role for $5HT_3$ receptors in some elements of fear processing. However other measures of emotional processing, for example the recognition of fearful facial expressions, may depend on different mechanisms; for example more interpretative strategies than the emotion potentiated startle, which is a more automatic process (Harmer et al., 2006b).

Conclusion

Increasing serotonin function by administration of *d*-fenfluramine, results in decreased levels of dysfunctional attitudes in healthy subjects. Also,

high serotonin receptor binding potential is associated with more dysfunctional attitudes in depressed individuals, but not in healthy subjects and borderline patients with a history of self-harm. These results are not confounded by any effects on mood. A study on the effects of ondansetron suggests a role for $5HT_3$ receptors in other, more automatic aspects of fear processing. $5HT_2$ and $5HT_3$ receptors may thus play separate roles in the effects of serotonergic manipulations on mood and cognition.

Tryptophan augmentation studies

Increasing serotonin function by raising plasma levels of its precursor tryptophan can be achieved with different methods. Tryptophan loading studies mostly administer L-tryptophan intravenously or orally. Plasma tryptophan levels can also be elevated through administration of alpha-lactalbumin, a milk whey rich in tryptophan (Heine et al., 1996). Both methods have proven to be effective in raising plasma tryptophan levels and the ratio of tryptophan to the large neutral amino acids (LNAAs). Compared to casein (placebo), a diet rich in alpha-lactalbumin was found to increase the plasma tryptophan/LNAA ratio by 73.8% (Merens et al., 2005). Alpha-lactalbumin improved memory scanning in healthy, stress-vulnerable subjects compared to placebo (Markus et al., 2002) and improved abstract visual memory and slowed simple motor performance, without affecting mood in both recovered depressed patients and healthy controls (Booij et al., 2006a). Attenburrow et al. (2003) investigated the effects of an 80% tryptophan powder derived from milk whey (approximately 1.8 g tryptophan) on facial expression recognition in healthy females. This resulted in enhanced recognition of fear and happiness compared to placebo. These results are similar to the effects of acute SSRI administration on recognition of fear and happiness (Harmer et al., 2003a).

The results are also in line with the effects of a fourteen days intervention with tryptophan in healthy volunteers by Murphy et al. (2006) who found that the recognition of happiness was increased and the recognition of disgust was decreased, but only in females. Tryptophan administration also decreased attentional vigilance toward negative stimuli as well as baseline emotional startle response. Mood was not affected, neither was the level of dysfunctional attitudes (Murphy et al., 2006).

Luciana et al. (2001) compared the effects of tryptophan loading with the effects of tryptophan depletion on cognitive functioning, mood and neuroendocrine measures (prolactin and cortisol) in healthy participants. Tryptophan loading impaired working memory performance of negative stimuli and fine motor coordination and improved immediate vigilant attention. Both tryptophan loading and depletion resulted in a slight decrease of positive affect, leading the authors to conclude that the observed changes in cognitive function were not related to any changes in mood. However, because of a lack of a placebo condition, the results of this study may be inflated.

Conclusion

In healthy subjects enhancement of the serotonin precursor may lead to impaired affective working memory but also to enhanced attention and recognition of fear and happiness. Sub-chronic effects include an increased recognition of happiness and a decreased recognition of disgust as well as a decreased processing of negative stimuli. These cognitive changes seem to be unrelated to changes in mood. Tryptophan loading seems to have a broader range of effects on cognitive performance compared to the effects of receptor-agonist and -antagonist administration.

Acute tryptophan depletion studies

Experimental depletion of the serotonin precursor tryptophan has been found to decrease plasma tryptophan levels by 70-90% in 5-6 hours (Young et al., 1989). Acute tryptophan depletion (ATD) is therefore a useful tool to investigate the effects of lowered serotonin function in humans. ATD results in a temporary depressive relapse in 50-60% of recovered depressed patients taking serotonergic antidepressants (Delgado et al., 1990; Van der Does, 2001a). In healthy subjects, only small mood effects are found and particularly in subjects with a family history of affective disorders (Ellenbogen et al., 1999; Klaassen et al., 2002). In acutely depressed patients, ATD did not worsen symptoms on the test day, however a delayed effect was observed the next morning in a minority of patients (improvement and worsening) (Delgado et al., 1994). A delayed mood improvement was also found in depressed patients treated with venlafaxine (Booij et al., 2005b). The effects of ATD on mood are congruent with the expected effects of lowered serotonin function. One question we aim to answer in this paper is whether the same is true for the cognitive effects following ATD.

Tryptophan and cognitive performance are associated in a complex manner: differential results are observed across cognitive functions and subject groups. Experimental manipulations of tryptophan seem to affect temporal and frontal cognitive functions (memory consolidation and working memory for example) in opposite ways. ATD affects the processing of neutral information in healthy subjects; it especially impairs memory consolidation and improves focussed attention (Harrison et al., 2004; Riedel et al., 1999; Schmitt et al., 2000). These effects have been repeatedly reported and support a specific role for serotonin in memory and learning and not in executive (frontal-lobe) functions. However, because of the variation in cognitive tests used, drawing

strong conclusions on the effects of ATD on cognitive function remains problematic.

Effects of ATD in healthy subjects

A wide range of studies have been done on the cognitive effects of ATD in healthy participants but only a few reported effects of ATD that were dependent of the emotional valence of the stimuli. Murphy et al. (2002) found slowed responses to happy but not sad target words in the affective go/no-go task following ATD in healthy female volunteers. ATD also slowed responding in a visual discrimination and reversal learning task, in absence of a change in mood. These findings were in line with an earlier study that found increased reaction times for happy but not sad targets in depressed patients compared to healthy controls (Murphy et al., 1999). Rubinsztein et al. however did not find a differential effect of ATD on target valence using the same affective go/no-go task (Rubinsztein et al., 2001).

Harmer et al. (2003c) used a facial expression recognition task to test the effects of ATD in healthy subjects. Two competing hypotheses were formulated by the authors. The first stated that since administration of an SSRI resulted in increased fear recognition, ATD should result in *decreased* fear recognition (Harmer et al., 2003a). However, since acute administration of an SSRI can have the paradoxical effect of decreasing synaptic serotonin levels through activation of auto-receptors, ATD may also result in *increased* recognition of fear. Results showed that, ATD decreased the recognition of fear, but only in females. The speed of recognition of fear was slowed in all subjects. No effects on mood were found. These results are in line with the finding that increased serotonin function increases the processing of fear. As a possible explanation for the specific effects in women, the authors noted that

the effects of ATD on mood are also greater in women, possibly resulting from greater reductions in serotonin synthesis following ATD in women compared to men (Ellenbogen et al., 1996; Nishizawa et al., 1997). One methodological remark should be made regarding this study. The effects of ATD on the accuracy of facial emotion recognition may have been even more complex. The interaction effect of emotion x drink in females was not significant (p = 0.1). However, separate analyses per emotion revealed a significant effect of ATD on fear recognition. In males the interaction effect of Emotion x Drink was also not significant (p = 0.13). However, no separate analyses were performed in this group, suggesting that a significant effect of ATD on one of the emotions in males may have been overlooked. Looking at the graphic display of the accuracy data, ATD may have increased the recognition of anger and surprise in males.

Park et al. used a variety of neutral tests and found that ATD selectively impaired learning and retrieval in healthy male volunteers. However, no effect was found on the specificity of autobiographical memory (Park et al., 1994). Coull et al. (1995) found that, using an emotional selective attention task, ATD reduced reaction times to incompatible stimuli but this effect was independent of the emotional valence of the distractor words. Evers et al. found that speed of delayed recognition on a verbal learning task was slowed following ATD, but again no differential effect was found for word valence (Evers et al., 2005). In another study ATD improved performance on a neutral Stroop task but increased the interference for negative words in an emotional Stroop task (Evers et al., 2006). Hayward et al. also found an increased negative attentional bias in healthy subjects in response to ATD, together with an enhanced recognition of happiness (Hayward et al., 2005). These results are in

line with result from studies in depressed patients, showing an emotional processing bias towards negative stimuli (e.g. Murphy et al., 1999).

Effects of ATD on decision making

Rogers et al. (1999a) used a gambling task to investigate the effect of ATD on decision making in healthy subjects. Results showed that tryptophan depleted subjects had an increased tendency to choose the least probable outcome and a trend toward increased deliberation times compared to the placebo group. These impairments partly resembled the performance of amphetamine abusers and patients suffering from damage to the orbitofrontal-prefrontal cortex. Results from animal and human studies indicate that the difficulty with decision making in chronic amphetamine abusers may result from altered serotonergic modulation of the ventral PFC and its connected structures (Groenewegen et al., 1997; Hotchkiss & Gibb, 1980).

In a recent study on decision making by Rogers et al. (2003), a novel version of the gambling task was used that allows for an examination of separate mechanisms that play a role in decision making: the magnitude of expected gains and losses and the probability to which these outcomes are delivered. ATD resulted in an impaired capacity to discriminate between magnitudes of expected gains, associated with different choices. ATD was not associated with altered discrimination between the magnitudes of expected losses, or altered discrimination with the relative probability with which these positive or negative outcomes occurred. Risk-averse and risk-seeking bias were also unaffected by ATD. The authors concluded that decreased serotonin function leads to altered modulation of cortical and subcortical regions that mediate important aspects of associative learning. They suggested that decision making may be influenced by monoaminergic systems, possibly involving

changes in the modulation of the prefrontal cortex and the limbic-striatal circuit.

Another study investigated the effect of ATD on decision making, using the same gambling task as Rogers et al. and ID/ED attentional set shifting in healthy subjects (Talbot et al., 2006). Contrary to previous results, ATD *improved* decision making (subjects chose the more likely outcome more often following ATD compared to placebo). There was no effect of ATD on set-shifting, reversal learning, risk taking, impulsivity or mood. The contradiction between these results and the results of the Rogers et al studies (1999a; 2003) was suggested to be due to possible influences of trait characteristics of the individuals tested, such as aggression and genetic factors associated with a family history of alcoholism. Also, genetically determined variations in the effects of ATD on ventral PFC function (e.g. decision making) caused by, for example, serotonergic polymorphisms were suggested to play a role. Finally, there were differences between the studies in the exclusion of hormonal contraception, the permission of smoking and small differences in age and IQ (Talbot et al., 2006).

Anderson et al. (2003) studied the effects of ATD on an imaginary gambling task in healthy subjects. No effects of ATD were found on the performance on this task, but the imaginary nature of the gambling task raises the question of whether this test is comparable to computerized gambling tests.

These studies emphasize the need for further investigations of the role of serotonin in decision making. Other factors possibly confounding the contradictory results should also be investigated: e.g. characteristics of the subject sample such as age and gender; differences in design –between- or within-subjects- and task difficulty.

In healthy volunteers with and without a family history of affective disorders (FH+ and FH-) the effect of ATD on memory bias and mood was investigated (Klaassen et al., 2002). ATD led to a significant lowering of mood (at 6 hours after ingestion of the drink), especially in the FH+ subjects. ATD impaired the recall of neutral words (6 hours after ingestion of the ATD drink) and positive words (at +24 hours), but not of negative words in all subjects. There was no association between mood and affective memory bias. However, ATD did impair delayed recall for neutral words more in mood-responders (all FH+ subjects) than in non-mood responders. The authors suggested that depressed mood did not seem to mediate the cognitive disturbance. Also, since only delayed recall was affected, ATD seems to selectively influence consolidation and not retrieval.

Effects of ATD in remitted and recovered depressed subjects

Booij et al. (2005a) investigated the effects of a full strength tryptophan depletion drink compared to a quarter strength mixture (high-dose vs. low-dose) on mood and cognitive function in medicated remitted depressed patients. The low-dose tryptophan depletion mixture consists of the same amino acids as the high-dose mixture, but at quarter strength following the method of Krahn et al. (1996). Most studies included in this review use a tryptophan containing amino acid mixture as a placebo (Murphy et al., 2002; Park et al., 1994; Rubinsztein et al., 2001) which causes a marked but highly variable increase of tryptophan levels. This means that most studies use an active condition rather than a neutral control condition, which is important when investigating subtle effects. A low-dose tryptophan mixture is also not a neutral procedure but results in a predictable moderate reduction of the tryptophan/LNAA ratio. Since the low-dose mixture has been found not to

affect mood (Booij et al., 2005a), it allows for an investigation of the dose-response effects of lowered serotonin function and thus is a better control condition for some research questions.

Following high-dose ATD, a subgroup of patients experienced a temporary depressive 'relapse' (: responders) (Booij et al., 2005a). The processing of positive material was impaired independent of mood change, whereas in another study in healthy subjects ATD impaired attention for negative words (Evers et al., 2006). Attention for neutral stimuli improved in a dose-dependent manner in all patients, which is in line with the effects of ATD in healthy subjects (Evers et al., 2006). The authors suggested that ATD may affect mood and cognition through different pathways; one implicated in mood and the processing of emotional information and one implicated in the processing of neutral information. In another study, high-dose ATD decreased immediate recall of positive words in responders but not in non-responders. Also, high-dose ATD tended to decrease the consistency of positive trait ratings compared to low-dose ATD, but again only in responders (Booij et al., 2005c). Another study investigated the effects of ATD in unmedicated recovered depressed patients and healthy controls (Hayward et al., 2005). The recovered depressed subjects showed an elevated startle response, impaired short-term memory, increased negative attentional bias and impaired recognition of happy facial expressions. Independent of the effects of ATD, the recovered depressed subjects showed enhanced recognition of disgust compared to healthy controls and a lack of a positive bias in the recall of emotionally valenced words. No changes in mood were found following the low-dose tryptophan depletion.

Munafò et al. (2006) studied the effects of ATD on the processing of social threat cues in medicated and unmedicated recovered depressed subjects

and healthy controls. Compared to a control drink, the tryptophan depletion mixture increased the processing of social threat cues on an Emotional Stroop Task in the medicated recovered depressed subjects, as shown by an increased interference. In this group, also a small but significant increase in self-rated depression scores was found. The tryptophan depletion mix did not affect mood and emotional processing in healthy volunteers and unmedicated depressed subjects. The authors explained the effects by suggesting that ATD may remove the neurochemical support of continued medication usage among this group. Also, the two recovered depressed groups may differ in their underlying vulnerability to decreases in serotonin function. Important to note is that the medicated patient group in this study was not selectively treated with SSRIs but with different kinds of serotonergic antidepressants (eg. also tricyclic antidepressants); however patients taking selective noradrenergic medication were not included.

Conclusion

ATD affects a broad range of cognitive functions, both in healthy volunteers and in remitted depressed patients. However, not all functions are affected and there are between-group differences in effects. In healthy subjects, ATD affects facial emotion recognition, attention for neutral stimuli and attentional bias, in absence of any mood effects. ATD seems to impair decision making in healthy subjects, however results are conflicting. ATD lowered mood in FH+ subjects and impaired the recall of neutral and positive words, but not of negative words in both FH- and FH+ subjects. In recovered depressed subjects, ATD increased depressive symptoms and affected the processing of positive material; attention for neutral stimuli; startle response, initial memory, attentional bias; the recognition of happy facial expressions and

the processing of social threat cues. No relationship between changes in mood and emotional information processing was found, except for the decreased recall of positive words following ATD in remitted depressed patients.

Discussion

The framework of this review is the theory that cognitive changes mediate the clinical effects of antidepressants. Three assumptions underlying this theory were formulated.

The first assumption is that serotonin manipulations (including the administration of antidepressants) have reliable effects on cognition. In this context, the following aspects of emotional functioning have been investigated:

Results from several studies suggest a role for serotonin in the *recognition of facial expressions of emotions*, especially fear. These results have been found across a range of different procedures, however the effects on fear processing appear to be dependent on the length of treatment: In healthy subjects, an acute increase in serotonin function elevated the recognition of fear and happiness (Attenburrow et al., 2003; Bhagwagar et al., 2004; Harmer et al., 2003a), after seven days the recognition of fear and anger was decreased (Harmer et al., 2004; Harmer et al., 2006a), and after fourteen days the recognition of happiness was increased and the recognition of disgust was decreased in females (Murphy et al., 2006). The effects on fear processing also appear to be affected by vulnerability to depression: in recovered depressed individuals, a decreased recognition of fear was found following a single SSRI administration (Bhagwagar et al., 2004), which is contrary to the increased fear recognition found in healthy volunteers. In line with expectations, the effects of ATD seem to be opposite to those of acute SSRI- and tryptophan administration: ATD decreased the recognition of fear in healthy females but

not in men (Harmer et al., 2003c) and impaired the recognition of happiness in both healthy and recovered depressed subjects (Hayward et al., 2005). The reported differences between acute vs. sub-chronic administration and between different samples appear to be important and need further investigation since the underlying mechanisms are still unclear.

Different studies investigated the effects of ATD on *attentional bias* using the Stroop test. Studies differed in the type of test (colour naming or counting) and type of stimuli (neutral and emotional; masked or unmasked) that were used. Despite these differences, the results are rather consistent. Attention for neutral stimuli is improved by ATD in both healthy women and recovered depressed subjects, as shown by a decreased interference for incongruent stimuli (Booij et al., 2005a; Evers et al., 2006). However, ATD has been found to increase attentional bias for negative stimuli in both healthy and recovered depressed subjects (Evers et al., 2006; Hayward et al., 2005; Munafò et al., 2006). Only in medicated recovered depressed subjects, this was accompanied by an increase in subjective depression (Munafò et al., 2006). One study found an increased interference for positive material in recovered depressed subjects following ATD, independent of mood change (Booij et al., 2005a). Following fourteen days of tryptophan administration, a reduced attentional vigilance to negative words was found (Murphy et al., 2006). Overall, lowered serotonin function is found to improve attention for neutral stimuli and to increase attentional bias toward emotional stimuli in both healthy and recovered depressed subjects. Increased serotonin function may have the opposite effect.

Several studies have shown that serotonin manipulations affect *emotional memory* in healthy and recovered depressed individuals. Lowered serotonin function impairs the memory of positive material; increased

serotonin function improves the memory for positive material and impairs the memory for negative material. (Evers et al., 2005; Harmer et al., 2004; Klaassen et al., 2002; Luciana et al., 2001). Only one study found a link between serotonin induced changes in mood and recall for positive material (Booij et al., 2005c). However some studies reported negative results (Harmer et al., 2006b; Hayward et al., 2005).

Serotonin is suggested to play a role in *decision making* in healthy individuals, but results have been contradicting, perhaps due to methodological differences (Anderson et al., 2003; Rogers et al., 1999a; Rogers et al., 2003; Talbot et al., 2006).

Interestingly, higher serotonin receptor binding potential was associated with unfavorable scores on *dysfunctional attitudes* in healthy volunteers, currently depressed (Meyer et al., 2003) and recovered depressed patients (Bhagwagar et al., 2006). Fourteen days of tryptophan administration in healthy subjects had no effect on dysfunctional attitudes (Murphy et al., 2006).

The effect of serotonin manipulations on attentional bias is most robust. The role serotonin plays in the processing of facial expressions of fear and other emotions however needs further investigation since differences exist in the effects of acute vs. sub-chronic administration and between different samples. These differences appear to be important however the underlying mechanisms are still unclear. Therefore, future research, preferably from different research groups, will need to verify the exact mechanisms with which serotonin is linked to the recognition of certain facial expressions and the direction of this association. The findings of a link between serotonin receptor binding potential and dysfunctional attitudes seem very promising for future research on the biological correlates of emotional information processing.

Serotonin is also suggested to affect decision making and emotional memory; however more research is needed to clarify the role serotonin plays in these cognitive processes. In particular, it is unclear whether these effects are limited to certain serotonin manipulations and/ or certain study samples. The effect of serotonin on the specificity of autobiographical memories has only been investigated in healthy individuals and remains uncertain.

The second assumption stated that the cognitive effects of serotonin manipulations are also observed in currently depressed subjects starting antidepressant treatment. Only one study on the effects of SSRIs on emotional information processing in currently depressed patients could be found (Fava et al., 1994). However, this study did not assess acute and short-term cognitive changes but only performed pre- and post treatment assessments. It is therefore not suitable for our review. Evidence from other studies also indicates that dysfunctional attitudes decrease following antidepressant treatment, however these studies did not primarily investigate selective serotonergic antidepressants, but mainly cognitive therapy and tricyclic antidepressants (Beevers et al., 2003; DeRubeis et al., 1990; Peselow et al., 1990; Simons et al., 1984). These results suggest that similar cognitive changes occur following cognitive as well as pharmacological treatment. Of note is that these studies have only looked at dysfunctional attitudes and not at the more automatic aspects of emotional information processing. It may well be that early in treatment, changes in for example attentional bias occur, which may relate to subsequent clinical improvement. Future research should investigate the effects of different antidepressant treatments on various forms of emotional information processing.

Some indirect evidence also exists on the link between serotonin and emotional information processing in depressed patients. An fMRI study in depressed patients found increased left amygdala activation in response to masked emotional faces, especially fearful faces. This was normalized following an eight week treatment with the antidepressant sertraline (Sheline et al., 2001). Since the amygdala plays a central role in the processing of emotions, especially fear, these results suggest that serotonergic antidepressants may exert their effects in part by normalizing dysfunctional emotional processing.

The third assumption stated that the cognitive effects of antidepressants predict clinical response. No studies were found that investigated this assumption. Fava et al. (1994) found that the decreased level of dysfunctional attitudes following eight weeks of fluoxetine treatment was unrelated to symptomatic improvement. However, since only pre- and post treatment assessments were obtained, the temporal and causal relationship between cognitive changes and subsequent symptom change could not be explored, which makes this study unsuitable to investigate the third assumption. Simons et al. did find a link between cognitive changes and symptomatic improvement, and this was true for both cognitive therapy and tricyclic antidepressants (Simons et al., 1984). However, this study is also less suitable since it used the same design as Fava et al. and selective serotonergic antidepressants were not investigated. Various other studies looked at the mechanisms of change of pharmacotherapy compared to cognitive therapy (DeRubeis et al., 1990; Hollon et al., 2005; Rush et al., 1981). These studies have found that changes in cognition do not relate to subsequent changes in symptoms among pharmacotherapy patients, although substantial cognitive changes do occur. The authors explain this by the fact that in

pharmacotherapy, cognitive changes are not accompanied by the use of cognitive and behavioural strategies (e.g. meta-cognitive monitoring) (DeRubeis et al., 1990). However, besides cognitive measures that assess the goals of cognitive therapy (e.g. dysfunctional attitudes) other forms of emotional processing (e.g facial expression recognition, attentional bias) may also be relevant to study during treatment. Since dysfunctional attitudes have been found to be linked to serotonin receptor binding potential (Bhagwagar et al., 2006; Meyer et al., 2003), other forms of emotional processing may as well have serotonin-related correlates in the brain. In order to investigate the causal relationship between cognitive changes and subsequent symptomatic improvement, mood and (different types of) emotional information processing should be assessed regularly during the first two months of antidepressant treatment.

The evidence discussed in this review is limited by the absence of studies in currently depressed patients. The large variety of cognitive tests makes it hard to draw definite conclusions. Most studies did not report power analyses and almost all studies are based on small sample sizes. However, the quality of the reviewed studies in terms of the methodology is satisfactory. Studies are comparable since most studies used a between-group design and matched their groups for age, gender and IQ or level of education. One study only included men (Park et al., 1994) whereas other studies only included women (Attenburrow et al., 2003; Bhagwagar et al., 2004; Evers et al., 2006; Harmer et al., 2003a; Murphy et al., 2002), thereby possibly influencing results since serotonin synthesis differs between females and males (Nishizawa et al., 1997).

Regarding the quality of the decision making studies, two inconsistencies should be noted. First, Anderson et al. (2003) used an imaginary gambling task instead of a computerized test, which may have caused the negative results. Second, despite of using the same gambling task, Talbot et al. (2006) found that ATD *improved* decision making in contrast to the *impaired* decision making found by Rogers et al. (1999a; 1999b). The authors suggested a few explanations for this inconsistency (see Results section under *Effects of ATD on decision making*), however both studies seem to be set out equally well, and further replications are necessary

The ATD studies differed in design (parallel or cross-over) and the exact depletion method used (amount of amino acids, amount of tryptophan added to the control mixture, adherence to a low-tryptophan diet before the session). These differences may have influenced results, for example in the case of control mixtures in ATD studies that increased plasma tryptophan levels, thereby increasing the contrast between ATD and the control procedure. Some studies used low-dose ATD as a control mixture (Booij et al., 2005a; Hayward et al., 2005; Munafò et al., 2006). However, the studies of Hayward et al. and Munafò et al. reported large decreases in plasma tryptophan following their low-dose and may better be referred to as high-dose ATD (Merens & Van der Does, 2007).

Although the hypothesis that cognitive effects of antidepressants predict clinical outcome is as of yet unsupported, there are promising directions for future research. Serotonin is certainly involved in various aspects of emotional information processing. However, a link between serotonin induced changes in mood and changes in emotional information processing has not been established. To fully explore this link, future research should be directed at currently depressed patients. Furthermore, studies should include

immediate as well as sub-chronic and long-term measurements of different aspects of emotional information processing to clarify a possible mediating role of cognitive changes in clinical outcome, as well as the pattern of change. Different cognitive domains are worth investigating, especially attentional bias, facial emotion recognition, decision making, dysfunctional attitudes and emotional memory. Studies should combine various outcome measures to investigate the effects of antidepressant treatment on different forms of emotional information processing. Subjective and objective mood measures should be obtained in order to make comparison between studies in healthy and (recovered) depressed patients possible. Also, apart from serotonergic antidepressants, other antidepressant treatments may be included to investigate possible common effects on emotional information processing and their underlying mechanisms.