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PII: S0163-7258(18)30232-8
DOI: https://doi.org/10.1016/j.pharmthera.2018.12.010
Reference: JPT 7315

To appear in: *Pharmacology and Therapeutics*

Please cite this article as: Beata R. Godlewska , Cognitive neuropsychological theory: Reconciliation of psychological and biological approaches for depression. Jpt (2018), https://doi.org/10.1016/j.pharmthera.2018.12.010

P&T 23346

Cognitive neuropsychological theory: reconciliation of psychological and biological approaches for depression

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Abstract

New antidepressants and individualized approaches to treatment, matching specific therapies to individual patients, are urgently needed. For this, a better understanding of processes underpinning the development of depressive symptoms and response to medications are required. The cognitive neuropsychological model offers a novel approach uniquely combining biological

and psychological approaches to explain how antidepressants exert their effect, why there is a delay in the onset of their clinical effect, and how changes in emotional processing are an essential step for a clinical antidepressant effect to take place. The paper presents the model and its underpinnings in the form of research in both healthy and depressed individuals, as well as the potential for its practical use.

Keywords: cognitive neuropsychological model, negative bias, emotional processing, antidepressant response

Abbreviations

CBT cognitive-behavioral therapy

dlPFC dorsolateral prefrontal cortex

ECT electroconvulsive therapy

(f)MRI (functional) magnetic resonance imaging

5-HT1A serotonin type 1A receptor

mPFC medial prefrontal cortex

NRI norepinephrine reuptake inhibitor

(pg)ACC pregenual anterior cingulate cortex

SNRI serotonin-norepinephrine reuptake inhibitor

SSRIs selective serotonin reuptake inhibitors

tDCS transcranial direct current stimulation

TMS transcranial magnetic stimulation

1. Introduction

Efficacious pharmacological treatments for depression have been used since the serendipitous discoveries of the first monoamine oxidase inhibitor (MAOI), iproniazid, and the first tricyclic antidepressant (TCA), imipramine, in the 1950s (López-Muñoz and Alamo 2009) followed by the development of a psychological approach specifically targeting depression, cognitive-behavioral therapy (CBT), in the 1960s (Beck 1967). Developments of new drugs, such as selective serotonin reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors

(SNRIs), and new psychological approaches followed, having a dramatic effect on the lives of millions of depressed individuals afflicted by this previously untreatable condition (López-Muñoz and Alamo 2009). Curiously, for a long time practitioners favouring pharmacological or psychological therapies seemed to be unable to find a common language, at times approaching open animosity. Recent years, however, have witnessed a change in this regard, with rapidly developing conversations between followers of biological and psychological theories, stimulated and facilitated by the development of research tools allowing exploration and a better understanding of biological underpinnings of emotional and cognitive processes, and the impact of antidepressants on both biological processes and psychological function.

This has led to the development of new platforms for understanding of the pathogenetic mechanisms of depression and antidepressant drug action, opening new avenues for explorations of crucial clinical issues. Novel perspectives were indeed urgently needed given a large number of depressed patients not responding to their first – or indeed never responding to – antidepressant treatments (Warden et al. 2007). New drug development and matching treatments to individuals have become critical clinical issues.

2. Cognitive neuropsychological hypothesis

An important shift in the perception of psychological and biological elements not as separate entities but as processes influencing and complementing each other, led to the development of an influential hypothesis of antidepressant drug action, the so-called cognitive neuropsychological hypothesis (Pringle et al. 2011, Roiser et al. 2012, Warren et al. 2015). This model attempted to answer the question why commonly used antidepressant medications take weeks to induce a clinically significant change in mood. This is particularly intriguing as changes in

neurotransmitters occur within hours of treatment initiation and strongly suggests that for the clinical effect, a change in monoamine levels is not sufficient and other processes must take place. The model hence challenges the monoamine hypothesis of antidepressant drug action and suggests that there may be multiple 'points of entry' downstream in the process that could serve as alternative targets for therapeutic agents.

What are the main assumptions of the cognitive neuropsychological theory? The key hypothesis of the model is that in order to achieve mood improvement, a change in emotional processing, resulting in a reduction of the negative biases that characterise depression, needs to take place. This is however insufficient to induce clinical improvement. For that, environmental and social interactions are needed to stimulate a learning process, leading to development of new more positive associations and subsequent mood improvement. The time needed for this process can explain the delay in the antidepressant effect. The cognitive neuropsychological model is schematically presented in Figure 1.

The important part of the hypothesis, i.e. that changes in the emotional bias affect mood only if there are interactions with the environment, needed to be tested. A study in healthy individuals showed that after 7 days of treatment with either citalopram or placebo, in the absence of any baseline mood change, people treated with citalopram were not affected by a negative mood induction (Browning et al. 2011). The extent of the protective action against negative mood was inversely correlated with the effect of the drug on emotional memory. In line with the hypothesis, another study in depressed patients with late-life depression, showed a predictive therapeutic effect of early bias shift only in patients who perceived their level of social support as adequate (Shiroma et al. 2014).

3. The principal components of the cognitive neuropsychological hypothesis and depression

The cognitive neuropsychological hypothesis in a novel way combines two components, equally important for antidepressant drugs action, an affective-cognitive and a neural process, and proposes how they interweave to produce antidepressant effect (Pringle et al. 2011). The following two paragraphs briefly discuss affective-cognitive and neural dysfunction in depression, to provide the context for the cognitive neuropsychological model.

3.1.The affective-cognitive component in depression

Depression is characterised by a number of cognitive distortions while perceiving and processing internal and external stimuli, which facilitate the development and maintenance of depressive symptoms (Roiser and Sahakian 2013, Robinson and Roiser 2016). One of the most robust and consistently observed distortions, which is the focus of the cognitive neuropsychological hypothesis, is the negative bias in information processing in depression. Already in 1976, Aaron Beck proposed the concept of the depressive 'negative triad', irrational, negative views about oneself, the world and the future, reinforcing one another and enhancing negative belief systems in depression (Beck, 1976). A change in negative bias is one of the main goals of CBT, a validated psychological treatment, widely used in depression.

Research has consistently supported negative bias as a one of the core psychological dysfunctions in depression (Mathews and MacLeod 2005, Gotlib and Joormann 2010). The processing of social cues and self-related information is particularly affected, especially if the stimuli are emotionally loaded. Tasks involving recognition of facial emotions and testing memory of, and attention to, self-referential information, have been successfully used as probes

in experimental conditions. Facial emotion recognition tasks seem to be particularly sensitive probes, which is not surprising as the ability to correctly recognize human emotions is fundamental to social interactions and as such, essential to human well-being (Pringle et al. 2015). Negatively biased recognition and interpretation of facial emotions may lead to the development of a sense of living in an unfriendly social environment, resulting in mood impairment and/or maintenance of depressive symptoms. The examples of findings include, among many others, preferential recall – immediate and delayed – of mood congruent negative information in free recall tasks, decreased memory for positive information , excessive processing and facilitated integration of negatively valenced emotional information of a personal nature, increased identification of negative emotions in faces, and an impaired recognition of facial emotional expressions in general, with a specific enhancement of the recognition of sadness (Roiser and Sahakian 2013, Warren et al. 2015).

3.2.The neural component in depression

With the development of imaging techniques such as magnetic resonance imaging (MRI) or positron emission tomography (PET), it was possible to explore the mechanisms of bias formation at the neural level. Research dating back to the early 1990s (Mayberg 1997) led to the formulation of one of the most prominent etiopathological models of depression (Drevets 2001, Mayberg 2003). This model proposes the inability of frontal cortices to control overactive limbic structures, responsible for the quick automatic processing of emotionally salient information, as the central dysfunction, offering biological ‘scaffolding’ for negatively biased processing of emotional stimuli. In depression, an exaggerated response to negative emotional stimuli has been repeatedly shown in parts of the limbic system, such as the amygdala and anterior cingulate cortex (ACC), while decreased responses were observed in dorsolateral prefrontal cortex

(dlPFC). This way negative information processing prevails over positive, which is one of the important factors in the formation and maintenance of depressed mood (Rive et al. 2013). This model, most relevant for the cognitive neuropsychological hypothesis, is complemented by other models. For example, hyperactivity in the default mode network, involved in internally oriented attention and self-referential thinking, might facilitate integration of negatively biased information (Whitfield-Gabrieli and Ford 2012).

4. Testing the validity of cognitive neuropsychological hypothesis: effect of short-term antidepressant treatment on emotional processing and negative bias

Antidepressant treatments have been repeatedly shown to reverse neural abnormalities characterizing depression (Wessa and Lois 2015). One of their key effects is a restoration of the top-down equilibrium, through attenuation of exaggerated limbic response and a recovery of an appropriate activity in the frontal structures. In this manner antidepressants change the balance in the processing of negative versus positive stimuli and remove the functional neural 'scaffolding' for negative bias formation. The attenuation of response to emotionally salient stimuli was shown to be most robust in the amygdala and ACC, consistent with the fronto-limbic model of depression and bias formation. Other structures are also the target of antidepressant medications, including the insula and striatum. Most studies examining the impact of antidepressants employed a longitudinal design, with a baseline assessment before treatment initiation, and a follow up after 6-12 weeks, corresponding to the time at which therapeutic response is clinically determined (eg. Sheline et al. 2001, Fu et al. 2013a, Williams et al. 2015).

These findings are highly informative about the neural mechanisms through which antidepressant drugs may exert their effects; however, they are unable to provide an insight into

why there is a delay of onset of the therapeutic effect. In particular, they cannot answer the question of whether a positive shift in emotional processing at behavioural and neural levels is a consequence of mood improvement, ie. people feel better and therefore negative bias decreases, or if mood improves as a result of the changes in how the brain processes information. The latter possibility, as mentioned above, is the key idea of the cognitive neuropsychological model, which has been tested in a number of studies. Initially its validity was explored in healthy volunteers, and subsequently in depressed subjects. A summary of the behavioural and functional neuroimaging effects of acute and short-term antidepressant administration and non-pharmacological treatments on measures of emotional processing in healthy volunteers, individuals with high neuroticism, depressed patients and recovered depressed patients in shown in Table 1.

4.1.Research in healthy volunteers (unselected population and individuals with high neuroticism)

Research in healthy volunteers was critical for the disambiguation of the effect of mood. Most studies included healthy individuals as defined by no present or past history of mental health disorders, including depression, while a minority used a different approach, focusing on a selected group of healthy people with high neuroticism scores, who show neural and cognitive biases in emotional processing, typical for depression but without other symptoms of the condition, i.e. depressed mood, memory and executive function deficits. High neuroticism scorers because of their cognitive-emotional profile, are good models for an assessment of effect of treatments on biased information processing without the influence of clinically depressed mood.

Numerous behavioural and functional imaging studies in never depressed healthy individuals, showed that commonly used antidepressant medications decreased response to aversive stimuli, mainly fear but also anger and disgust, and increased processing of positive emotions, without any effect on mood. The changes were observed early on in the course of treatment, after 7-10 days (eg. Harmer et al. 2004, Harmer et al. 2006, Murphy et al. 2009), or even after a single dose of medication (eg. Harmer et al. 2003, Del-Ben et al. 2005, Harmer et al. 2006, Norbury et al. 2007, Anderson et al. 2007, Browning et al. 2007, Miskowiak et al. 2007, Bigos et al. 2008, Harmer et al. 2008, Harmer et al. 2009, Murphy et al. 2009, Arnone et al. 2009, Norbury et al. 2009, Rawlings et al. 2010, Anderson et al. 2011, Grady et al. 2013, Kalkulainen 2017). A robust neural effect was consistently observed in the amygdala and the ACC, and also seen across a network of structures, including medial prefrontal cortex (mPFC), insula, orbito-frontal cortex, striatum, thalamus and dlPFC. A meta-analysis by Ma et al. (2015) lent support to smaller single studies, showing a decrease in reactivity to negative facial expressions across a network of brain regions including the amygdala, ACC, putamen, parahippocampal gyrus and mPFC (Ma et al. 2014).

The results of behavioural studies were less uniform. One possible explanation is that tasks assessing behavioural effects of medications are less sensitive than neural probes. Although recognition of happiness was shown to increase in some studies, both an increase and decrease in recognition of negative emotions (fear, disgust and anger) were observed. An increase in fear recognition seemed to be, however, present for SSRIs only, and only after a single dose of the drug, not after 7 days (e.g. Harmer et al. 2003, Browning et al. 2007, Grillon et al. 2007, Bigos et al. 2008 , DiSimplicio et al. 2014). This phenomenon may be linked to the anxiogenic effect of

SSRIs, which is a relatively common side-effect observed at the beginning of treatment, and which usually subsequently resolves.

This effect of citalopram was explored in a recent PET study (Selvaraj et al. 2018). In healthy individuals who received citalopram infusion as compared to saline there was an enhanced amygdala response to fearful vs neutral facial expressions. The availability of serotonin type 1A (5-HT1A) receptors in dorsal raphe nucleus correlated positively with the effect of citalopram on amygdala response, suggesting a key serotonergic mechanism behind increases in fear processing with SSRIs, and lending support to a role for 5-HT1A receptors role in mediation of emotional processing.

Word categorisation and emotional recall studies showed, respectively, shortening of response time to, and increased recall of, positive versus negative words, although some studies yielded no significant effect at all (Murphy et al. 2006, Browning et al. 2007, Miskowiak et al. 2007, Harmer et al. 2008). Both behavioural and neural effects were seen across different antidepressants and their classes, including SSRIs citalopram, escitalopram, and fluvoxamine, a norepinephrine reuptake inhibitor (NRI) reboxetine, an SNRI duloxetine, and atypical drugs, such as mirtazapine (Komulainen et al. 2016) or agomelatine, a melatonin agonist (Harmer et al. 2004, Harmer et al. 2011). The importance of this fact and potential applications will be discussed further in the paper.

Interestingly, in participants with high neuroticism, short-term citalopram treatment increased processing of all emotions, negative and positive, perhaps reflecting reduced avoidance of experimental emotional stimuli. Increased positive emotional recognition after an acute dose (Jonassen et al. 2014) and increased amygdala response to fearful, happy and neutral emotions

after 7 days of treatment (DiSimplicio et al. 2014) were all observed. The studies also showed both shorter (Jonassen et al. 2014) and longer (DiSimplicio et al. 2014) gaze maintenance at facial expressions after, respectively, an acute dose and 7 days of treatment. This could be explained by an acute anxiogenic effect of selective serotonin reuptake inhibitors (SSRIs), as discussed, followed by its abolishment and consequently improved engagement with social stimuli.

4.2.Research in depressed individuals

The findings in healthy volunteers have shed light on the early effect of antidepressants on behavioural and neural processing of emotionally salient information, without depressed mood acting as a confounder. The next step was investigating whether there was a causal relationship of this early change in biases with the later improvement in clinical symptoms in patients suffering from clinical depression. To address this question, we designed a functional magnetic resonance imaging (fMRI) study, which assessed a change in neural response to fearful versus happy emotional expressions in depressed patients over seven days of treatment with the SSRI escitalopram (Godlewska et al. 2016).

Two fMRI assessments were performed, one before treatment was started and the other after 7 days, with severity of depression being measured at baseline, after 7 days and 6 weeks of treatment. At baseline, depressed patients showed a greater activation than healthy individuals to fearful versus happy faces in the left insula and ACC. After 1 week of treatment, a decrease in reactivity across the number of structures, including the left amygdala, insula, anterior and posterior cingulate, bilateral supramarginal gyri and bilateral thalamus was seen. Importantly, it was notably greater in individuals who went on to respond to treatment at 6 weeks, as compared

to week 6 non-responders, suggesting that this early change might be necessary for antidepressant action. Crucially for the cognitive neuropsychological model, in over 7 days of treatment no clinically significant change in mood was observed and the difference in clinical ratings between 6 weeks responders and nonresponders was not statistically significant, despite the fact that numerically a decrease in HAMD scores was larger in responders. An inclusion of baseline depression severity and depression change over the first 7 days of treatment as a covariate, had no effect on the fMRI results. Secondary mediation analysis supported independence of the effect from any influence of early mood change.

A recently published study (Komulainen et al. 2018) in 32 depressed patients randomized to escitalopram 10 mg or placebo for one week supported our findings. Similar to our study, assessments were performed after 7 days of treatment, at which point there were no significant differences in mood between the two groups, while changes at the neural level were observed. In more detail, escitalopram treatment led to a decrease in response of medial fronto-parietal regions to self-referential emotional words relative to non-emotional control stimuli, and an increase in the mPFC and ACC to positive relative to negative words. This again implies a direct effect of escitalopram on emotional processing rather than a direct effect on mood.

Effects of short-term antidepressant treatment on emotional processing in depressed individuals were also tested in a number of studies using behavioural tasks, and their results were consistent with the findings of imaging studies. A single dose of reboxetine was shown to increase recognition of happy facial expressions and recall of positive versus negative emotional words (Harmer et al. 2009). In another study, seven days of treatment with 10mg of citalopram increased recognition of happy faces (Shiroma et al. 2014), while 14 days' administration of both citalopram 20mg (Tranter et al. 2009) and reboxetine 4mg (DiSimplicio et al. 2014) was

associated with not only an increase in the recognition of happy faces, but also of disgust and surprise. These changes in emotional processing were seen in the absence of significant mood change.

An important question when considering the results of the above studies is whether observed effects could be attributed to repeated psychological testing rather than to the action of the drug. In the study by Kalkulainen et al. (2018) using a placebo-controlled design, the neural change related to the positive shift in bias was seen only in the escitalopram group. The drug effect in our study (Godlewska et al. 2016) was supported by the results from a previous study in which 42 unmedicated depressed patients were randomized to 10 mg escitalopram daily or placebo (Godlewska et al. 2012). After seven days of treatment, the amygdala response to fearful facial expressions was higher in depressed patients who received placebo as compared to active treatment, while no difference between the escitalopram treated group and healthy volunteers was seen. This suggested that short-term escitalopram treatment had 'normalised' the exaggerated amygdala response to fear in the depressed patients. At this point, as well as at baseline, the escitalopram and placebo treated groups did not differ in terms of clinical depression scores. The findings support the notion that escitalopram, but not placebo, affects emotional processing. Another recent study (Huneke et al. 2017), using a validated battery of emotional processing tasks, the Emotional Test Battery, compared the effect of placebo to no treatment in healthy participants and showed no significant differences between the groups on measures of emotional processing. In the same study, comparison of the above groups to a group treated with buproprion showed no effect of subjective treatment expectancy on task performance. This study lends support to the notion that effects observed in the above discussed studies in depressed individuals can be attributed to drug action and not to a placebo effect.

In summary, the above studies, by showing changes in emotional processing towards a reduction in negative bias early in the course of treatment, in the absence of mood changes, support the cognitive neuropsychological theory of antidepressant drug action.

4.3.A note on delay in onset of antidepressant action

Until recently it has been widely accepted that antidepressants take a few weeks to work, and this notion has had a strong influence on designing research projects, the development of clinical guidelines and everyday clinical practice (Mitchell 2006). However, the last decade has witnessed an emergence of studies suggesting that non negligible improvement occurs over the first few days of treatment, and that it continues to build up over the following several weeks (eg. Taylor et al. 2006). In our studies testing the validity of the cognitive neuropsychological model in depressed patients, responders and non-responders did not differ significantly either before escitalopram was started or after 7 days of treatment, while changes in emotional processing were already noticeable (Godlewska 2012, Godlewska 2016). The change in depression scores was not significantly different between the placebo and antidepressant-treated groups; in both groups scores decreased after a week of treatment, and more so numerically in 6 weeks responders. In the context of the above work on the delay of the onset of antidepressant effect, this opens an interesting area for exploration within the model. Hypothetically, it is possible that an early symptomatic improvement may depend on an even earlier shift in the emotional bias, which gets reinforced over time in treatment responders. At this point this is purely speculative, as research on exploring this question in depressed patients is lacking. However, a shift towards more positive processing of emotional information has been observed in healthy volunteers as early as after a single dose of antidepressants (Harmer et al. 2003, Harmer et al. 2003b, Harmer et al. 2008, Harmer et al. 2009, Murphy et al. 2009), and one session of electroconvulsive

therapy (ECT) (Miskowiak et al. 2017, 2018a, 2018b). This suggests that important changes in emotional processing may be taking place earlier than after 7 days of treatment, which – apart from one study (Harmer et al. 2009) –has been the earliest time-point assessed so far in depressed patients treated with antidepressants.

Exploring this issue might yield important implications for understanding of complex mechanisms underlying antidepressant action, allowing a better insight into relationships between drugs, biological and emotional-cognitive changes, and symptomatic improvement. However, for this to happen, a major shift in how depression is conceptualized is required, i.e. a shift from understanding it as a diagnostic entity towards a dimensional approach, allowing a more analytical approach to symptoms. At this point most research (including our own studies on early response to medication) still uses diagnostic categories and general improvement rather than changes in particular symptoms or their groups, and this is at least to some extent justified by clinical and translational needs. For patients a 'time to substantial improvement' is likely to be more important than an 'onset of action' and achieving 'some treatment response'. At the same time, a better understanding of early effects of antidepressants, their mechanisms leading to such effects and the implications for response prediction may prove highly useful clinically, and lead to tailored treatments (see a paragraph on 'precision psychiatry' below).

5. Can cognitive neuropsychological model be applied to non-pharmacological therapies?

A natural question is whether the cognitive neuropsychological model can be applied to treatments other than pharmacological ones. Although research exploring an influence of non-pharmacological modalities on emotional processing is much less abundant than in case of

pharmacological approaches, a few studies suggested that an early shift in emotional bias may contribute to future treatment effect with these treatment approaches too.

One of non-pharmacological approaches, used since 1938, and acknowledged as an effective therapy for treatment resistant depression, is electroconvulsive therapy (ECT). A few recent studies by one group of researchers revealed the effect of ECT on emotional processing after just one session. A single ECT session, compared to sham treatment, in 25 treatment resistant patients reduced neural response in the left frontopolar cortex to positive words in the retrieval-specific phase of the self-referential emotional word categorization test (Miskowiak et al., 2018a). The authors argued that this might represent early facilitation of memory for positive self-referential information and may be one of the mechanisms leading to mood and self-esteem improvement later in the course of treatment. In another study (Miskowiak et al. 2018b), a decrease in neural response to unpleasant vs. pleasant pictures in the medial prefrontal cortex was shown after one ECT session, suggesting modulation of medial prefrontal hyper-activity during encoding of negative affective information. In an earlier study (Miskowiak et al, 2017), using facial expression recognition task, no effect on amygdala reactivity was revealed for fearful vs happy contrast, while a change in neural response was seen in ECT but not sham treated patients in the parahippocampus, superior frontal gyrus, and in functional connectivity between amygdala and occipito-temporal regions. Additionally, a negative correlation between amygdala - occipital coupling and fear vigilance was observed. The authors emphasized that changes occurred ‘in the absence of differences in mood or behavioural performance between the groups’. These studies showed a shift in emotional processing very early in the course of ECT treatment, when no significant clinical effects were yet noted. This is interesting in the context of the following early symptomatic response for which ECT is known. Clinical studies have shown

that as many as 80% patients showed >50% decrease in HAMD after 6 ECT sessions, about 50% of patients already after 3 ECT sessions, with a small subgroup responding as soon as after one session (Fink 2014). How this early improvement might fit with the cognitive neuropsychological model has not been explored yet. Clinically ECT appears to have an early impact to decrease psychomotor retardation and improve motivation (Browning and Cowen, 1986). It is possible that such effects could help 'maximise' ECT-induced benefits in emotional processing by increasing the likelihood that patients will engage in positive social interactions early in treatment.

Recent years have witnessed a rapid development of non-invasive brain stimulation techniques, such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), both of which have been shown to be effective treatments for depression (Shiozawa et al. 2014). TMS and tDCS work through application of, respectively, a magnetic or electric current through the scalp, with electrodes placed over dlPFC, aiming at changes in neuronal excitability. Another non-pharmacological approach, albeit invasive and hence less feasible for clinical use, is deep brain stimulation (DBS), in which electrodes are implanted in the brain (Benabid et al, 2009).

As these are relatively new treatments, not much is known about their effect on emotional processing. However, a few recent studies showed that a single session of tDCS was able to reduce the negative processing bias in the absence of mood changes. For example, in healthy volunteers an improvement in recognition of both happy and fearful facial expressions, with more robust effect for positive emotion (Nietsche et al. 2012), as well as a reduction in attentional vigilance to threatening stimuli (Ironside et al. 2016), were observed. A study in a depressed population showed that one tDCS session modified negative attentional bias and

decreased response time for negative vs. positive words in an emotional Stroop task (Brunoni et al. 2014). These observations suggest that a single tDCS session is capable of inducing changes in emotional processing both in healthy participants and depressed patients. Although TMS changes emotional processing over the course of treatment, its acute effect is not yet elucidated. A DBS study showed that after 1 month of treatment, categorization of negative words as self-descriptive decreased; this was associated with a reduction in the P1 EEG component amplitude, corresponding to reduced attentional bias to negative words (Hilimire et al. 2015). After 6 months, there was a correlation between increased control over negative word, indexed by the P3 EEG component, likely reflecting reduction in more elaborative processing of negative stimuli, and reduced depression scores. These observations are of interest; however, the study concerned was small with only 7 patients included.

Another important group of therapies are talking therapies, with CBT being used commonly in depression. It is known that over the course of treatment, CBT leads to a shift in in emotional bias, which is indeed one of its key treatment goals. It was suggested that, in general terms, CBT works mainly by increasing top-down control in executive and dorsal attention networks, but also, although to a lesser extent, by reducing overreactivity of ventral cortico-limbic structures, the latter being main mode of action of pharmacological treatments (DeRubeis et al. 2008, Kalsi et al. 2017). Unfortunately studies investigating early shifts in emotional processing during CBT are scarce and were applied to panic disorder (Reinecke et al. 2014), not depression.

More studies in healthy volunteers and depressed patients mirroring a design used in drug studies, i.e. assessment at baseline, after acute or short-term treatment, and then at a time when clinical response is usually seen, are needed. However, the studies performed to date, through showing that a change in emotional processing predates a clinically significant mood effect,

suggest that the change in emotional bias may at least partly underwrite treatment effect of brain stimulation therapeutic interventions and CBT. This opens a window for further exploration of the cognitive neuropsychological hypothesis in this context.

6. Can psychological and pharmacological elements be reconciled in case of rapid-acting glutamatergic treatments for depression?

Ketamine, a non-competitive open channel NMDA (N-methyl-D-aspartate) antagonist, and an anaesthetic recently repurposed as an antidepressant, differs from other antidepressant medications in that it produces striking mood improvement within hours, often in people who were previously declared treatment resistant (Berman et al, 2000). Ketamine seems to share certain neurobiological actions with other antidepressants; however, the cascade of events is much faster, starting from a ketamine-triggered increase in glutamatergic neurotransmission leading to a rapid increase in extracellular glutamate levels, increase in brain derived neurotrophic factor (BDNF), changes in signalling cascades, protein production, and synaptogenesis, followed by mood improvement in the course of hours (Duman et al, 2016; Li et al, 2010; Rantamäki and Yalcin, 2016).

This rapid antidepressant effect of ketamine poses a challenge to the application of the cognitive neuropsychological model, which emphasises the need for learning processes following a shift in emotional bias, over a period of time. Although the pattern specific for ketamine is not yet elucidated, it is known that this agent, similar to other medications with antidepressant potential, produces a shift in emotional bias both at behavioural and neural levels (Scheiddegger et al, 2016a). Studies showed, for example, a decrease in amygdalo-hippocampal reactivity to

emotional stimuli (Scheiddegger et al, 2016b) and modulation of cognition-emotion interaction (Scheiddegger et al, 2016a).

Recently a plausible explanation has been proposed for how changes in emotional processing fit both the delayed-onset effect of conventional antidepressants, and the rapid but temporary antidepressant effect of ketamine (Stuart et al, 2015, Harmer, 2017). Experiments in rodents allowed a comparison of venlafaxine and ketamine on the affective bias associated with learning, and on the modification of previously acquired biases (Stuart et al, 2015). It was shown that venlafaxine, but not ketamine, increased acquisition of positive bias (i.e. learning of positive affective information), while ketamine, but not venlafaxine, attenuated the previously acquired negative bias (i.e. it abolished memory for previously acquired negative memory associations). At the neural level, the ketamine effect was mapped to the mPFC, while that of venlafaxine involved amygdala.

This finding requires replicating, yet it is an intriguing possibility that while conventional antidepressants might work through the formation of new positive associations, with a necessary step of time-requiring interactions with the environment, ketamine might be able to reduce or abolish already existing negative encodings, for which environmental interactions would not be needed, leading to a faster onset of clinical effect, which then however dissolves after a few days. In this context, it might be of interest that recent work showed that prophylactic use of ketamine reduced fear response in mice (McGowan et al., 2017), and that this action was mediated by ventral CA3 hippocampal subfield (Mastrodonato et al., 2018). Also, hippocampal neurogenesis, one of the biological effects of antidepressant drugs, was shown to reduce generalization and long-term retention of aversive memories in animal models (Drew and Huckleberry 2017). Currently a lot of attention has been attracted by a newly developed

intranasal forms of ketamine, which may facilitate its clinical use, and hydroxynorketamine, an active metabolite of ketamine, which acts directly on AMPA receptors and, while being easier to use, in theory might produce fewer side-effects (Zarate and Niciu, 2015; Zanos et al, 2016, Zanos et al. 2018). The hypothetical place of rapid acting antidepressants within the cognitive neuropsychological model is schematically presented in Figure 1.

7. Can response to treatments for bipolar depression be understood within the frame of the cognitive neuropsychological model?

Impairments in the processing of emotions in bipolar depression have been covered by excellent reviews (eg. Strakowski et al. 2012) and their presentation is beyond the scope of this paper. It is however an intriguing question - whether response to treatments for bipolar depression can be conceptualized within the same frame of the cognitive neuropsychological model as response to antidepressants in major depressive disorder. Unfortunately, at this point there is no data that would allow formulating evidence-based conclusions, and the situation is further complicated by the uncertain efficacy of conventional antidepressant medication, such as SSRIs, in bipolar depression.

In addition, to the author's best knowledge, there have been no studies testing an impact of broadly understood mood stabilizers (including lithium, antiepileptics and antipsychotics) on early changes in emotional processing in bipolar individuals. One study in healthy people showed that 150mg of quetiapine XL, as compared to placebo, had no impact on emotional processing in a majority of commonly used tests (facial expression recognition, emotional word categorisation, emotion-potentiated startle or emotional word/faces dot-probe vigilance reaction time), and the only positive finding related to diminished bias towards positive words and away

from negative words during recognition memory (Rock et al. 2016). Given a large number of studies suggesting a limited impact of mood-stabilizing medications on fMRI emotional processing (Hafeman et al. 2012), it is possible that such treatments exert their effect by other mechanisms. Research in this area is hampered by practical issues, such as recruitment of unmedicated bipolar individuals, and both ethical and scientific limitations related to applying a wash-out period.

8. Is reconciliation between biological approaches and cognitive neuropsychological hypotheses possible?

A number of biological processes have been shown to be triggered by antidepressant drug application, including changes in monoamine neurotransmission (Hamon and Blier 2013), glutamate excitotoxicity (Olloquequi et al. 2018), gene expression, transcription processes, 5-HT1A autoreceptor desensitization (Blier and de Montigny, 1998, Hensler 2003) and neuroplasticity (Liu et al. 2017), with a particular role for the BDNF signalling pathway (Castrén and Kojima, 2017). The time needed for some of these processes to emerge served as an explanation for the delayed onset of antidepressant effect. The cognitive neuropsychological theory, while it does not explore molecular phenomena in detail, proposes them as underpinnings for the neural changes and relearning processes that result in acute emotional bias changes being translated into enduring mood improvement.

9. Potential applications of the cognitive neuropsychological theory

9.1.Development of new antidepressant treatments

An intriguing possibility is that the cognitive neuropsychological theory could be employed in the development of new antidepressants, and in the repurposing of already existing drugs. The benefits include a relatively simple, easily applicable design, and – provided that safety of the drug is established – its use directly in humans, which can be a more valid approach than using animal models. This way the high investment needed in drug discovery, unavoidable during the early clinical phases of drug development, could be directed towards most promising agents.

For this to happen it needs to be shown that the cognitive neuropsychological model allows for the differentiation of drugs with and without an antidepressant potential. The finding that a shift in emotional bias was present across different antidepressant classes, including SSRIs (citalopram and escitalopram), SNRIs (duloxetine), NRIs (reboxetine) and atypical antidepressants (mirtazapine and agomelatine), has been critical for moving this hypothesis forward.

There are also a limited number of studies which suggest that drugs lacking an ability to positively bias emotional processing in humans are likely to fail as useful clinical antidepressants. For example, a single dose of memantine, an NMDA antagonist used in Alzheimer's disease treatment, whose antidepressant potential was suggested by animal studies and an open-label trial, had no effect on emotional processing including facial emotion recognition and attentional vigilance to emotional words, while it enhanced the startle response (Sani et al. 2012, Pringle et al, 2012). In line with this, in randomized controlled trials memantine failed to produce an antidepressant effect (Zarate et al, 2006).

The neurokinin 1 (NK1) receptor antagonist aprepitant was another medication that attracted attention as a potential antidepressant agent because of promising effects in animal models of

depression. It received however mixed support from clinical trials, which hampered its progression into a licensed antidepressant medication (Keller et al, 2006; Kramer et al, 2004). Inconsistent clinical findings were mirrored by unclear results of emotional processing tests (McCabe et al, 2009, Chandra et al, 2010; Pringle et al, 2011; Harmer et al, 2013). For example, aprepitant enhanced the neural response in the ACC and amygdala to happy, but not fearful faces (McCabe et al, 2009); it increased recognition of happy faces and vigilance towards all emotional words, but had no impact on recognition of negative emotions, including fear; no effect on categorization or memory of emotional words was shown (Chandra et al, 2010).

Rimonabant is an inverse agonist of the cannabinoid receptor CB1 used as an antiobesity drug. Rimonabant is an interesting example how changes in emotional processing opposite to those characterizing clinically effective antidepressants, may indicate that a drug may actually have untoward effects on mood. In behavioural tests rimonabant was shown to reduce positive bias in healthy people, impairing recall of positive, while preserving that of negative words (Horder et al, 2009), and reducing the number of false recollections of positive words (Horder et al, 2012). This effect was observed both after a single dose and 7 days of treatment. Interestingly, rimonabant was removed from the market following reports of a high incidence of depressive symptoms, including suicidal ideation, in those who used it (Christensen et al, 2007). This suggests that negative changes in emotional bias might be useful to detect drugs that carry an increased risk of causing depression during their clinical use.

The model is promising, however, it needs to be better explored before its routine application to drug discovery, as is highlighted by confusing results produced for lanicemine (AZD6765). Lanicemine is a low trapping non-selective N-methyl-D-aspartate (NMDA) receptor antagonist, which initially suggested a similar antidepressant effect to that of ketamine while producing

fewer dissociative side-effects (Newport et al. 2015). However, despite possession of an antidepressant profile in neuropsychological studies (a decrease in amygdala responses during negative facial expression processing, and an increase in positive memory intrusions 24 hours post-infusion), inconsistent antidepressant effects were apparent and drug development did not progress beyond phase IIa (Sanacora et al. 2014, Sanacora et al. 2017, Harmer et al. 2017). As noted, although studies researching mechanisms of ketamine's effect on emotional processing are still scarce, findings open the possibility that glutamatergic agents exert their antidepressant effect through different psychological mechanisms than primarily serotonergic and noradrenergic drugs (i.e. transient 'forgetting' negative associations rather than learning new positive ones) (Stuart et al. 2015). If so, although standard emotional processing tests may indeed show early changes, they may be misleading in indicating a robust long term antidepressant effect. This warrants further research on this group of drugs.

An important issue to be taken into account is that additional factors may influence the effectiveness of the cognitive neuropsychological model. For example, it was shown that increased pretreatment dlPFC reactivity predicted the level of clinical improvement with antidepressant treatment but only in individuals with no history of childhood abuse (Miller et al. 2015), while in a late-life depression study, only patients perceiving their social circumstances as good, improved with antidepressant treatment (Shiroma et al. 2014). This means that contextual factors may have a significant effect on whether changes in emotional bias are translated into clinical benefit. Thus the model might lack robust predictive value if accidentally patients with a certain feature prevail in the tested group.

Another opportunity offered by the model is the development of non-drug based cognitive interventions that would decrease negative bias, resulting in attenuation of depression risk. In

support of this hypothesis, a computerized attentional bias modification was shown to decrease residual symptoms and the cortisol awakening response in remitted depressed patients, considered to be measures of recurrence risk in this group (Browning et al. 2011). Longitudinal studies are needed to assess validity of this approach.

9.2.Treatment response prediction and treatment stratification

Another important clinical application of the model is prediction of response to treatment. The need for biomarkers of response is urgent, given the burden of depression and the fact that even in the best case scenario, due to the delay of onset of the clinical effect, depressed individuals are required to wait a number of weeks before their mood improves significantly, and this period gets extended to months or even years for those who need multiple treatment attempts (Warden et al. 2007). Early treatment biomarkers could guide a choice between pharmacotherapy or psychotherapy, classes of medications, or, in the ideal world, point to an individual drug most likely to benefit a given patient.

Much research work over the past two decades has focused on identifying biomarkers of therapeutic response, however, no marker can yet be clinically applied. Presently, increased pretreatment reactivity of the pregenual ACC (pgACC) seems to be the most robust indicator of good future response across a variety of treatments – CBT, sleep deprivation, and different classes of antidepressants, regardless of the imaging technique and analytical approach used (Pizzagalli 2013, Fu et al. 2013a). Our recent studies have added to this body of evidence by showing that both baseline pgACC over-reactivity to emotional stimuli (Godlewska et al. 2018) and a decrease in this reactivity after 7 days of treatment (Godlewska et al. 2016) were indicative of treatment response after 6 weeks of escitalopram. Although a decrease in the pgACC activity

was previously observed in responders over 6-8 weeks of treatment (Arnone 2018), our study provides evidence for an early change in the pgACC activity. As a general response indicator, pregenual ACC reactivity may not be helpful in a choice of a particular treatment; however, it may be useful when identifying people with a poor prognosis who need a more intense therapeutic approach from the very beginning of therapy.

Interestingly, activity of the pgACC may also be relevant to the clinical response to glutamatergic antidepressants. Thus findings of a recent study (Downey et al. 2016) suggest that increased ACC reactivity may be necessary for treatment response. The authors reported that symptom reduction at 1 and 7 days after an infusion of the glutamatergic compounds, ketamine and lanicemine, was only present in depressed individuals in whom pgACC activity increased as a result of this infusion. It was suggested that glutamatergic drugs might act initially by switching the ACC into a treatment-responsive mode, in which state it would be able to restore balance between dorsal cognitive and ventral emotional processing pathways.

The relevance of pgACC for treatment response is likely to originate from its central position within neural circuits involved in emotional and cognitive processing. With its widespread anatomical and functional connections with the limbic system (emotional processing), ventral striatum (reward processing), hypothalamus (autonomic function) and dlPFC (cognitive control), pgACC represents a crucial hub for the correct top-down regulation of initial limbic responses; it is also one of the main hubs within the default mode network (DMN). Increased pre-treatment pgACC activity has been suggested to reflect more preserved fronto-cingulate function, with a greater ability for increased effort to provide top-down regulation of limbic regions; this increased activity would also favour adaptive self-referential processing over depressive brooding (Pizzagalli 2011).

Such a functional state could create a 'platform' favouring treatment response over non-response. A difference in the extent of change in neural responsivity to fearful vs happy facial expressions after 7 days of escitalopram treatment between 6 weeks responders and non-responders shown in our study (Godlewska et al. 2016) was not restricted to the pgACC but also present across the number of other structures (amygdala, insula, posterior cingulate, supramarginal gyri and thalamus). In the light of this observation, it may be hypothesized that a decrease in the pgACC reactivity could be linked to normalization of the activity in other structures, in particular the amygdala, which would remove the need for increased pgACC activity.

The cognitive neuropsychological model, by exploring a specific mechanism of antidepressant action, offers an alternative way of predicting treatment response. If an early change in emotional processing bias is crucial for antidepressant effect, it means that the lack of this effect should be related to lack of subsequent clinical response. Research in patients with depression supported this hypothesis. Results of our recent study (Godlewska et al. 2016), were consistent with earlier behavioural studies (Tranter et al. 2009, Shiroma et al. 2014). Tranter et al. (2004) showed that two weeks of treatment with an SSRI citalopram or the NRI reboxetine led to an improvement in the recognition of facial expressions of happiness, disgust, and surprise, with no further change from week 2 to week 6. Importantly, the extent of the improvement in the happy emotion recognition correlated with the clinical improvement after 6 weeks of treatment and was predictive of treatment outcome. Shiroma et al. (2014) in 72 patients with late-life depression treated with citalopram for eight weeks showed that after seven days of treatment, accuracy of happy emotion recognition predicted treatment response and remission at day 56, when considered along with perception of social support.

These studies in depressed patients indicate that an early change in emotional processing may be indeed one of the crucial events necessary for achieving response to antidepressant drugs. More research is needed to replicate these findings, and to investigate whether there may be differences specific to drug classes or individual treatments. A shift in emotional bias was observed after a single dose of treatment in healthy volunteer studies, and it is an intriguing possibility that a change after just one drug administration could be predictive of treatment response in depressed patients. Such studies have not been yet conducted.

Recent work shows a promise for more specific discriminatory effects. For example, a potential for discriminating between responders to pharmacotherapy or CBT was shown for baseline anterior insula metabolism (McGarth et al. 2013) or resting state functional connectivity (Dunlop et al. 2017). As currently people with depression are usually offered a pharmacological treatment first, knowing that some people are more likely to benefit from CBT would accelerate their access to the appropriate treatment. Some recent work also shows that markers of differential response to antidepressant classes, such as SSRIs and SNRIs (Gyurak et al. 2016), or even drugs within one class, such as escitalopram and sertraline as in case of the study by Williams et al. (2015), may be identified.

The notion that specific symptom groups may be particularly responsive to drugs that primarily target the putative mechanisms through which these symptoms develop, and its value for treatment management and drug development, has been explored within the cognitive neuropsychological model. Evidence-based theories propose that abnormal 5-HT neurotransmission may be primarily linked to the development of negative affect, experienced as sadness, while NA and dopaminergic (DA) dysfunction - to a loss of positive affect and anhedonia. NA neurotransmission has been suggested to be crucial for modulation and

enhancement of memories with emotional content, and as a consequence, that its dysfunction may have a negative impact on formation and maintenance of the positive affect (Pringle and Harmer 2011).

It has been proposed that drugs primarily enhancing 5-HT neurotransmission may act through decreasing negative affect, while those enhancing NA neurotransmission – often considered to be more effective than SSRIs against anhedonia and positive affect loss - may act by upregulating positive aspects of emotional processing (Pringle and Harmer, 2015). In line with this, the majority of studies testing the cognitive neuropsychological model in both healthy and depressed volunteers showed an early decrease in fear recognition and amygdala reaction to fearful faces following treatment with SSRIs citalopram and escitalopram, while an increase in the recognition of happy facial expressions was seen in those treated with an NRI reboxetine (see Table 1 for details). Only the minority of studies showed different effects (Table 1). This may have some practical implications. The findings support the importance of the personalized therapeutic approach and choice of treatments targeting prominent symptoms and their putative mechanisms of action. They may also play a role in new drug development, especially in case of compounds which mechanisms are not clearly understood. For example, if a new compound exerts a certain effect on emotional processing, it may suggest its potential usefulness against particular groups of symptoms. This hypothesis certainly needs more work but if proven correct, it would open an exciting possibility of using a simple emotional processing task to help identifying compounds worth time and resources needed for its development into clinically useful medications.

One of the frequently raised limitations to applying neuroimaging as a treatment biomarker in a clinical setting is the cost of this procedure, which would be doubled if two scans were needed:

one at a baseline and one after a few days of treatment. In that sense a single baseline marker of response, as tested in most studies, might be a preferable alternative. There is however a possibility that a baseline scan might not be necessary and that neural activity after a few days alone might be sufficiently informative of future treatment response. Indeed, in our study (Godlewska et al. 2016), differences at one week alone predicted response to escitalopram after 6 weeks. These predictors were seen across the same regions whose activity changed over 7 days of treatment (insula, thalamus, amygdala svc, thalamus and cingulate). In any case, given that depression is one of the economically burdensome health conditions, the scan costs are negligible compared to costs of absences from work and lower productivity, which could be saved if targeted treatment was started early; and this without even speaking about the personal burden to the individuals and their families.

10. Precision psychiatry and the cognitive neuropsychological model.

A better understanding of the mechanisms of action of antidepressants and response prediction fits into the increasingly emphasised need for 'precision psychiatry'. This concept embraces the notion of wide individual differences between patients depending on variability in genes, environment and lifestyle, which translates into variability in their needs and a necessity for a choice of interventions for which a likelihood of achieving responses will be high (Fernandes et al. 2017). Although psychiatry attempts to be 'personal', 'precision' in diagnosis and treatment has not been yet achieved.

An increased emphasis is currently placed on shifting the research focus from clinical diagnoses to domains defined by current understanding of biological (for example, genetic, molecular, cellular and neural) and behavioural underpinnings of emotion, cognition, motivation, and social

behaviour, with an acknowledgement of the role for environmental factors and space for subjective experience (for example, Research Domain Criteria (RDoC) (Insel 2014). Such an approach may subsequently lead to reformulation of what mental health conditions are and in time provide space for diagnostic and therapeutic approaches targeting specific pathologies in a very precise manner. This process has only just began, but new technological and analytical developments and new ways to conceptualize mental health problems, with intense research work taking place, suggest that this may change in the foreseeable future (Fu and Costafreda, 2013).

Recent work described in the section 9.2 presented some of the important recent neuroimaging contributions to this growing field, although the list is by no means exhaustive (eg. see Williams 2016). The cognitive neuropsychological model contributes an important role in the field, providing a new angle from which response to antidepressant treatments can be explored, as well as a more complex understanding of the events during the first few days of treatment both at the neural and behavioural level. As described above, it already allowed some insight into changes in the processing of specific emotions under the influence of particular drugs classes (ie. primarily targeting certain neurotransmitters), and attempts have been made to conceptualize this in the context of its meaning for clinical practice. Early changes in emotional processing have been shown to be predictive of future treatment response in depressed patients (Godlewska et al. 2016).

This is promising, however, more studies in depressed individuals are necessary to explore the potential of the model to best fit the demands of everyday clinical practice. For example, it will be important to explore at which time-point changes in emotional processing become informative of future response, to define which characteristics of these changes may be indicative of

particular classes of drugs – or indeed individual medications – being effective for an individual, depending on the profile of their symptoms, and to explore early changes in emotional processing in the relation to symptom dimensions, and time-points when particular symptoms start responding. In order to facilitate clinical implementation of the findings it would be useful to explore differences in sensitivity of neural measurements of emotional processing and out-of-scanner assessments; the latter would be more easily applicable and hence more useful in clinical scenarios. A necessary further step to fulfil the criteria of 'precision psychiatry' is an integration of findings with those from other models exploring emotional and cognitive processing in depression (Malhi et al. 2015), as well as with data from other fields, such as genetics.

Before this happens, the use of traditional diagnostic categories is still useful, and indeed may be necessary in the clinical settings, to provide as good management of depression as it is possible with currently available tools. Acceptance of new ways of managing depression – and other psychiatric conditions – will largely depend on how convincing and applicable scientific findings are, hence intense work in this crucial area is warranted.

11. Conclusions

The cognitive neuropsychological model offers a novel approach to understanding how antidepressant drugs exert their effect. By combining biological and neural approaches, and exploring the concept of the bias in emotional processing at the behavioural and neural level, it offers a plausible explanation for the delay in antidepressant drug action and is a step forward in developing the individualized approach to treatment. The practical application requires further work to address important questions about the kind of changes necessary for the clinical effect and the correlation between the extent of changes and the intensity of antidepressant responses.

Rapid developments of computational methods (Adams et al. 2016) hold a promise for the development of algorithms that can be useful in refining of the understanding of emotional processing inputs and applied in the clinical settings, for example, to match patients to specific treatments (Fu and Costafreda 2013, Warren et al., 2015). Translation of the findings into clinically applicable and useful tests for depressed patients would be a transformational step in treatment.

Acknowledgements

The author would like to thank Prof. Philip J Cowen and Prof. Catherine J. Harmer for fruitful discussions regarding the content of this paper.

Conflict of Interest statement

Dr B R Godlewska's salary is supported by Medical Research Council. She has received travel expenses from Janssen UK.

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Table 1. Effects of acute and short-term antidepressant administration and non-pharmacological treatments on measures of emotional processing in healthy volunteers, individuals with high neuroticism, depressed patients and recovered depressed patients: behavioral and functional neuroimaging findings. Arrows indicate increases or decreases in reported measures. Blank boxes indicate that a measure was not taken. Only significant findings are reported. BOLD response was recorded while viewing emotional facial expressions and arrows indicate decreases or increases in responses to a given emotion in reported brain structures. Medications given orally unless otherwise stated. Abbreviations: RT, reaction time; R, right, L, left; pos, positive; neg, negative; HC, healthy controls; RD, recovered depressed; PO, *per os*, i.e. taken orally; IV, intravenous; Amy, amygdala; OFC, orbito-frontal cortex; MFG, middle frontal gyrus; mPFC, medial prefrontal cortex; ACC, anterior cingulate cortex; PCC, posterior cingulate cortex; Ins, insula; Hipp, hippocampus.

Study	Medication and dose	Behavioral findings			Functional neuroimaging findings
		Self-referential processing (attention and memory)	Emotional facial expression (happy, fear, sadness, anger disgust, neutral) recognition accuracy	Emotion potentiated startle response	
HEALTHY VOLUNTEERS					
Acute studies: testing after a single oral dose or a single infusion (IV) of an antidepressant medication, or a single tDCS session					
Harmer et al. 2003	Citalopram 10mg IV		↑ happy, fear, with shift to lower intensity levels		
Del-Ben et al. 2005	Citalopram IV 7.5 mg over 7.5min				↓ aversive (anger/disgust/fear): R Amy, R lateral OFC ↑ aversive: R L fusiform gyrus, R L thalamus
Murphy et al. 2006	Citalopram 20mg PO		↑ happy		↓ fear in R Amy

Browning et al. 2007	Citalopram 20mg	Attentional visual probe: ↑ attentional bias to positive words	↑ fear	↑ irrespective of valence	
Anderson et al. 2007	Citalopram IV 7.5 mg over 7.5min				↓ fear: R Amy ↓ disgust: L Amy ↑ disgust: posterior Ins
Bigos et al. 2008	Citalopram IV 20mg over 30 min				↑ general emotional salient stimuli (anger/fear/surprise), drug concentration dependent: Amy
Harmer et al. 2003	Reboxetine 4mg	↓ RT to pos vs neg, and ↓ recall of negative, self-descriptors	↑ happy, with shift to lower intensity levels		
Miskowiak et al. 2007	Reboxetine 4mg	↓ RT to pos self-descriptors			
Harmer et al. 2009	Reboxetine 4mg	↓ RT to pos self-descriptors	↑ happy		
Harmer et al. 2008	Duloxetine 60mg	↑ in false positives recollection	↑ happy, disgust		
Arnone et al. 2009	Mirtazapine 15mg	↓ RT to pos AND neg (marginal), and ↑ recall of pos vs neg, self-descriptors	↓ fear	↓	
Rawlings et al. 2010	Mirtazapine 15mg				↓ fear, ↑ happy: R Amy-Hipp and L fronto-striatal regions ↓ fear vs happy: fusiform gyrus
Komulainen et al. 2016	Mirtazapine 15mg				↓ responses to self-referential

					processing: mPFC, ACC ↓ responses to POS self-referential processing: PCC, parietal cortex
Nietsche et al. 2012	tDCS 1 session		↑ happy, fear (happy more robust)		
Ironside et al. 2016	tDCS 1 session		Attentional visual probe (emotional facial expressions): ↓ attentional vigilance to fear		
Short term studies: testing after 7 days of treatment unless otherwise stated					
Harmer et al. 2004	Citalopram 20mg	↑ recall of pos vs neg self-descriptors	↓ fear, anger, disgust, surprise	↓ to neg pictures	
Harmer et al. 2006	Citalopram 20mg		↓ fear		↓ fear mPFC (BA 10), L Amy-Hipp area (whole-brain) Bilateral amygdala (ROI)
Murphy et al. 2009	Citalopram 20mg		Attentional visual probe (emotional facial expressions): ↓ attentional vigilance to fear		
Harmer et al. 2009	Citalopram 20mg 7 to 10 days				↓ fear Amy–Hipp area, MFG
Norbury et al. 2009	Citalopram 20mg 7 to 10 days				↑ happy L R Amy (ROI)

Maron et al. 2015	Escitalopram 10mg				↓ fear: L R Amy, ACC, R MFG
Harmer et al. 2004	Reboxetine 4mg	↓ RT and ↑ recall of pos vs neg self-descriptors	↓ fear, anger	↑	
Norbury et al. 2007	Reboxetine 8mg				↓ fear: R Amy ↑ happy: R fusiform gyrus
Murphy et al. 2009	Reboxetine 8mg				
Murphy et al. 2006	Tryptophan 3g	Attentional visual probe: ↓ attentional vigilance to negative words in females only	↑ happy, ↓ disgust in females only	↓ in females only	
Harmer et al. 2011	Agomelatine 25mg and 50mg	↑ recall of pos vs neg self-descriptors (25mg only)	↓ sad (25mg only)	↓ to neg and ↑ to pos pictures (25 and 50mg)	
INDIVIDUALS WITH HIGH NEUROTICISM					
Di Simplicio et al. 2014	Citalopram 20mg, 7 days		↑ gaze at facial expressions irrespective of valence and intensity ↑ pos vs neg, with shift towards lower intensity levels		
DiSimplicio et al. 2014	Citalopram 20mg, 7 days				↑ happy, fear, neutral: Amy fear vs happy: PFC

DEPRESSED PATIENTS (time of treatment reported by individual studies)					
Shiroma et al. 2014 – see note 1) below	Citalopram 10mg, 7 days		↑ happy		
Tranter et al. 2009 – see note 2) below	Citalopram 20mg, 14 days		↑ happy, disgust, surprise		
Godlewska et al. 2012	Escitalopram 10mg, 7 days				↓ fear: R amygdala ROI
Godlewska et al. 2016 - see note 3) below	Escitalopram 10mg, 7 days				> ↓ in response to fearful vs happy facial expressions across ACC, Ins, Amy and thalamus in 6 weeks responders vs non-responders
Komulainen et al. 2018	Escitalopram 10mg, 7 days				↓ self-referential vs non-emotional words: medial fronto-parietal regions ↑ pos vs neg words: mPFC, ACC
Tranter et al. 2009	Reboxetine 4mg, 14 days		↑ happy, disgust, surprise		
Harmer et al. 2009	Reboxetine 4mg, single dose	↓ RT to, and recall of, pos self-descriptors	↑ happy		
Delaveau et al. 2016	Agomelatine, 7 days				↓ self-referential processing: dlPFC
Miskowiak et al. 2018a	ECT, single session				↓ response to retrieval of positive word: L frontopolar cortex
Miskowiak et al. 2018b	ECT, single session				↓ response to unpleasant vs. pleasant pictures: mPFC

Brunoni et al. 2014	tDSC, single session	↓ neg attentional bias ↓ RT neg vs pos words in emotional Stroop task			
REMITTED DEPRESSED PATIENTS					
Anderson et al. 2011	Citalopram IV 7.5 mg over 7.5min, single infusion				RD vs HC: ↓ fear R L Amy ↑ happy: L ACC ↓sad: R posterior Ins, R lateral OFC HC vs RD: ↑ happy R L Hipp ↑ sad R anterior Ins

TREATMENT RESPONSE PREDICTION:

1) Shiroma et al. 2014: Change in emotion processing between baseline and day 7 predicted antidepressant response at day 56 if considered along with perceived level of social support.
2) Tranter et al. 2014: There was a significant correlation between the increased accuracy in recognition of happy faces over the first two-weeks of treatment and the clinical improvement after six-weeks of treatment
3) Godlewska et al. 2016: Degree of change in neural processing of fearful vs happy facial expressions across a network of structures including ACC, Ins, Amy and thalamus predicted response after 6 weeks of treatment.

Figure 1. Schematic presentation of the cognitive neuropsychological model of antidepressant action.

Depression is characterized by negative bias in the processing of emotionally salient information, resulting from the inability of frontal cortices to control overactive limbic structures, responsible for the quick automatic processing of emotionally salient information. The cognitive neuropsychological model proposes that antidepressants (ADs), by inducing neural and behavioral changes, cause a positive shift in emotional processing, and that this happens as early as the first few hours and days of treatment. However, in case of 'classical' ADs (i.e. the ones that take weeks to induce mood change, such as selective serotonin reuptake inhibitors (SSRIs) or selective serotonin reuptake inhibitors (SNRIs)), this is insufficient to induce clinical improvement. For that, environmental and social interactions are needed to stimulate the learning process, leading to the development of new, more positive associations and the translation of changes in emotional bias to improvement in mood. The model proposes that the time needed for this process explains the delay in the antidepressant effect. The model acknowledges the link between early biological changes and behavioral and clinical effects of ADs, with a place for continued downstream biological and neuroadaptive processes and a need for repeated administration of ADs. The hypothetical place of rapid acting ADs within the model is shown below the timeline. Early research allows for a tentative hypothesis that rapid acting ADs may act through reduction or abolition of negative associations, rather than learning new positive ones, hence no delay in their clinical effect on mood.

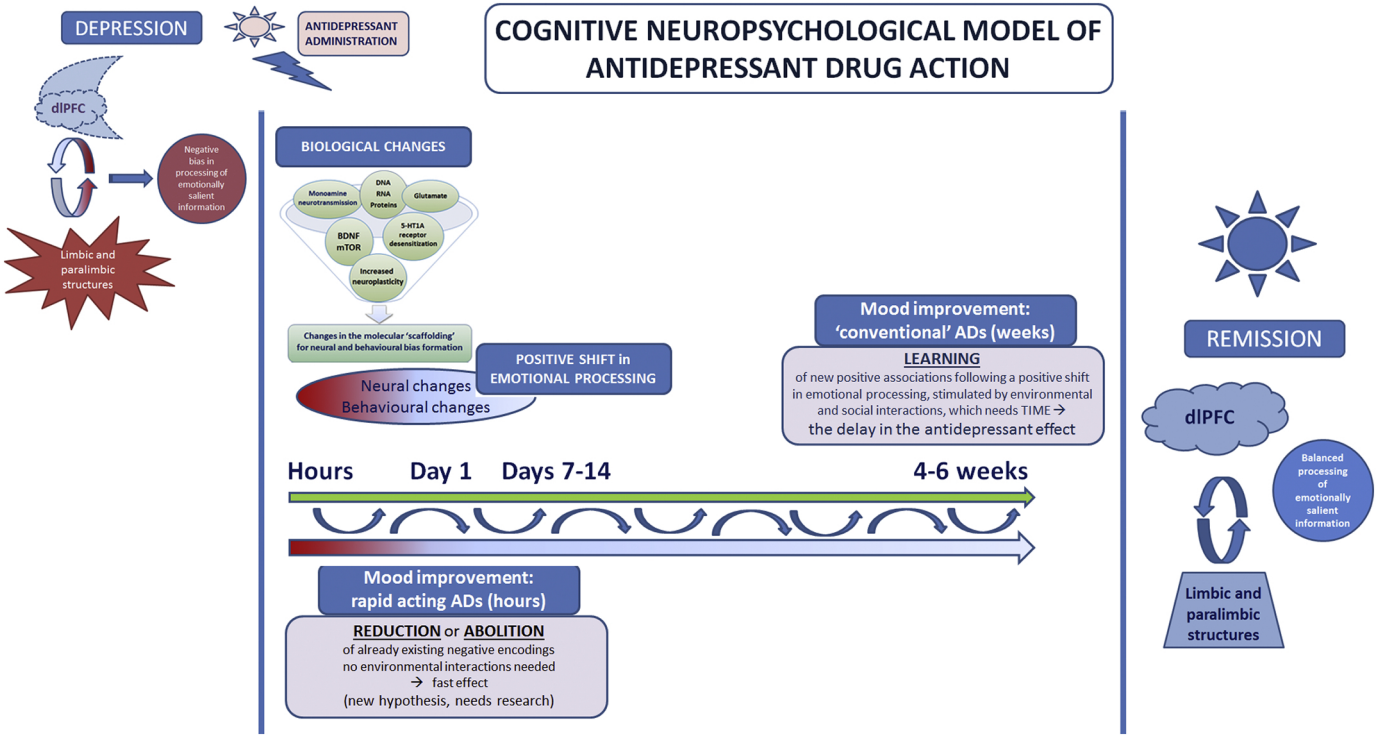
DEPRESSION
ANTIDEPRESSANT ADMINISTRATION
COGNITIVE NEUROPSYCHOLOGICAL MODEL OF ANTIDEPRESSANT DRUG ACTION
dlPFC
Negative bias in processing of emotionally salient information
Limbic and paralimbic structures
BIOLOGICAL CHANGES
Monoamine neurotransmission
DNA RNA Proteins
Glutamate
BDNF mTOR
5-HT1A receptor desensitization
Increased neuroplasticity
Changes in the molecular 'scaffolding' for neural and behavioural bias formation
POSITIVE SHIFT in EMOTIONAL PROCESSING
Neural changes
Behavioural changes
Mood improvement: 'conventional' ADs (weeks)
LEARNING
of new positive associations following a positive shift in emotional processing, stimulated by environmental and social interactions, which needs TIME →
the delay in the antidepressant effect
Hours
Day 1
Days 7-14
4-6 weeks
Mood improvement: rapid acting ADs (hours)
REDUCTION or ABOLITION
of already existing negative encodings
no environmental interactions needed
→ fast effect
(new hypothesis, needs research)
REMISSION
dlPFC
Balanced processing of emotionally salient information
Limbic and paralimbic structures

Figure 1