



A systematic review of the impact of social cognitive deficits on psychosocial functioning in major depressive disorder and opportunities for therapeutic intervention

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ABSTRACT

Social cognition is the ability to identify, perceive and interpret socially relevant information from the external world. It is an important adaptive trait, but is frequently affected in major depressive disorder by a mood-congruent interpretive bias. The present review examined the existing body of literature to determine (i) the impact social cognitive deficits in depression have on psychosocial functioning; and (ii) the utility of psychotropic, psychological and procedural interventions employed to target these deficits. A total of 107 studies met inclusion criteria for review. Social cognitive performance was found to adversely impact depressed patients' psychosocial functioning across the key domains of general cognitive functioning and quality of life. Secondly, many current therapies were found to have a normalising effect on the social cognitive abilities of subjects with major depressive disorder, both at a neural and functional level. In particular, certain anti-depressant medications corrected facial affect recognition deficits, while several psychotherapeutic approaches improved impairments in theory of mind and negative interpretive bias.

1. Introduction

The adaptive importance of social behaviours has long been the subject of academic interest. Darwin (1872) first explored the biological underpinnings of emotional behaviour in detail, while Ekman and Friesen (1971) later proposed six universal facial expressions that transcend cultural bounds. Contemporary research in this area focuses on what is now termed 'social cognition.' This is broadly defined as the way in which humans identify, perceive and interpret socially salient information. Social cognition therefore encompasses a wide range of verbal and non-verbal information, including facial expressions, prosody, body language and theory of mind.

The impact of major depressive disorder on social cognition is more nuanced than the profound performance deficits seen in other neuropsychiatric disorders, classically schizophrenia (Kandalft et al., 2012) and autism (Holdnack et al., 2011). It is now largely accepted that major depressive disorder is associated with a characteristic mood-congruent interpretive bias (Weightman et al., 2014). This manifests as depressed individuals displaying increased sensitivity for identifying

negatively valenced emotions and reduced accuracy for positive ones. Additionally, neutral stimuli are more likely to be assigned a negative interpretation. This pattern is consistent with cognitive theories of depression (Beck, 1963), which postulate that depressed individuals interpret social information through negative maladaptive schemata that then distort the perception of everyday interactions.

However, the clinical impact of this altered processing of socially relevant information in major depressive disorder is currently uncertain. Given its adaptive importance, deficits in social cognition are likely to have a deleterious impact on measures of general psychosocial functioning. Precise characterisation of this relationship will improve understanding of the morbidity of the disorder. Furthermore, if social cognitive dysfunction is shown to be clinically significant in major depressive disorder, there could be important implications for the development of specific interventions to target these deficits. The present review examines the existing literature with the aim of summarising (i) the impact of social cognitive deficits in depression on psychosocial functioning; and (ii) the utility of psychotropic, psychological and procedural interventions in their treatment.

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2. Methods

The protocol for this review of the literature was informed by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009).

2.1. Search strategy

An electronic search strategy was employed to identify published studies investigating social cognition in major depressive disorder between 1990 and 2018. Pertinent literature was identified and retrieved via the Medline, Embase, PsycINFO, PubMed, Scopus and Google Scholar databases. The search was limited to English language results only. The subject headings used across the different databases were ‘major depression,’ ‘depression,’ ‘depressive disorder,’ ‘mood disorder,’ ‘affective disorder,’ ‘social cognition,’ ‘affective cognition,’ ‘social function,’ ‘social perception,’ ‘social interaction,’ ‘interpersonal interaction,’ ‘theory of mind,’ ‘empathy,’ ‘facial affect,’ ‘facial expression,’ ‘facial recognition,’ ‘emotion,’ ‘emotion recognition,’ ‘empathy,’ ‘auditory perception,’ ‘speech perception,’ ‘prosody,’ ‘kinesics,’ ‘gesture’ and ‘body language.’ To maximise results, truncated search terms were included where possible and some subject headings were exploded to include narrower sub-headings. The searches using subject headings were supplemented by searches using similar keywords and phrases.

2.2. Study selection

The titles and abstracts of the results generated from the databases were collated and then screened to exclude irrelevant articles or duplicates. The full text of the remaining studies was downloaded and the methods inspected in detail to determine eligibility (Fig. 1). Studies were included in the analysis if they met the following criteria: firstly, the study group consisted of adult participants (> 18 years of age) with

diagnosis of major depressive disorder (MDD) made against standardised criteria. This included the *Diagnostic and Statistical Manual of Mental Disorders, IVth or 5th Editions* (DSM-IV/DSM-5; American Psychiatric Association, 2013) and the *International Statistical Classification of Diseases and Related Health Problems, 10th Revision* (ICD-10; World Health Organization, 1993), although administration may be via a standardised diagnostic procedure (e.g., the *Structured Clinical Interview for DSM-5*). Secondly, each study was required to investigate social cognitive performance in a recognised domain (e.g., facial affect, prosody, theory of mind). Thirdly, the study must also contain either (a) a measure of psychosocial functioning; or (b) have considered the effect of a pharmacological, psychological or procedural therapeutic intervention on social cognitive performance. Procedural interventions were defined as treatments that involve performing a physical procedure on a patient that is neither pharmacologically nor psychologically administered (e.g., neurostimulation).

Studies were excluded if the patient group had MDD as a secondary diagnosis (e.g., following a primary medical diagnosis) or was comorbid with a separate psychiatric disorder (e.g., schizophrenia, dementia, learning disorder, substance use disorder, eating disorder or pervasive developmental disorder). Studies were also excluded if the patient group demonstrated bipolar features. Studies were not excluded on the basis of including MDD patients with comorbid anxiety disorder, provided depression was the primary condition.

3. Results

3.1. Impact on psychosocial function

Social cognition is closely related to the concept of psychosocial functioning. The former is the mechanism by which socially relevant information is processed and used, while the latter describes more broadly the interaction between an individual and his or her

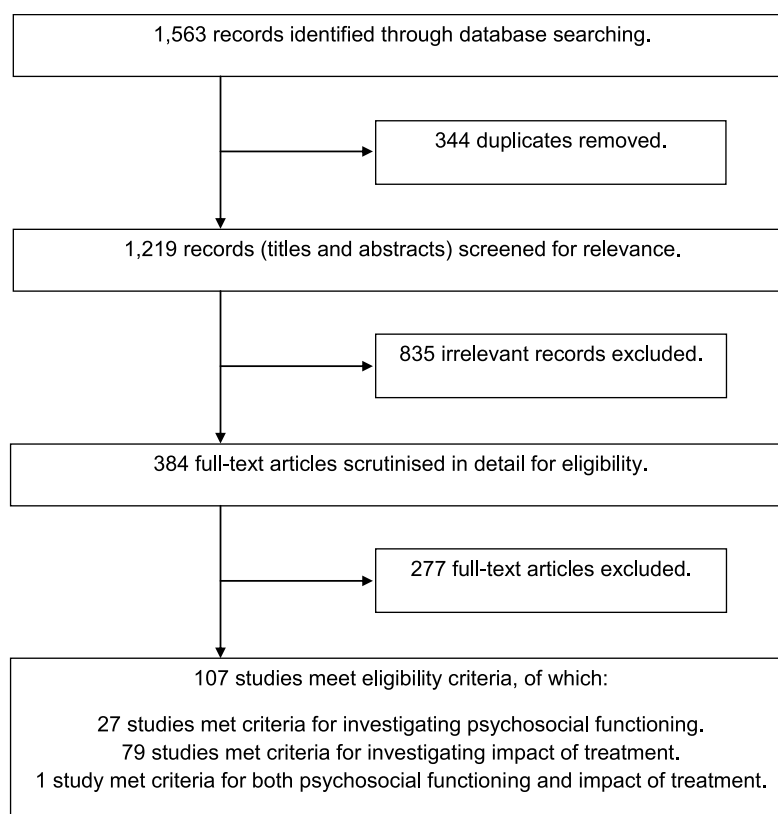


Fig. 1. Flowchart of article inclusion procedure during review of the literature. From 1563 individual records initially identified through the literature search of the Medline, PsychINFO, Embase and PubMed, Scopus and Google Scholar databases, 107 articles were included in the final analysis.

environment, including social interactions and interpersonal relationships (Ro and Clark, 2009). Some authors have attempted to quantify the impact of social cognitive impairments on the psychosocial functioning of those with a major depressive disorder. These findings are summarised below in the broad themes of social performance, emotional/empathic performance, cognitive functioning and quality of life.

3.1.1. Social performance

There is growing evidence that hostile and overly submissive interpersonal styles may reduce the quality of social interactions and contribute to the chronicity of major depressive disorders (Bird et al., 2018). While the present review did not identify any studies directly examining the link between social cognition and interpersonal style, findings proving indirect support for this relationship did emerge. For example, Szanto et al. (2012) demonstrated that older depressed participants with poor facial affect recognition demonstrated greater hostility and had smaller social networks, as characterised by poorer communication with family and fewer close friends, compared to those with greater affect recognition. Likewise, Derntl et al. (2011) found that depressed subjects demonstrated greater sensitivity to detect fearful emotions, as well as increased withdrawal towards emotional stimuli. While these results point to a negative contribution of social cognition on social performance, neither of these studies statistically evaluated the association between these features, underscoring the need for more research in this domain.

Depression appears to exert a negative effect on social problem solving ability (Thoma et al., 2015), which is a feature that may be explained mechanistically by poor social perception. Some support for this notion was found by Radke et al. (2013), who evaluated social problem solving ability using an electronic ultimatum game where affective facial expressions were paired to in-game offers. Depressed patients rejected a significantly higher percentage of offers than controls, suggesting that facial emotion was an important mediating factor in social decisions relating to fairness. These difficulties navigating social situations are hypothesised to contribute to low mood and diminished self-esteem. This explanation is consistent with behavioural theories of depression (Lewinsohn, 1974), where poor social outcomes reinforce maladaptive behaviours such as withdrawal or isolation and further perpetuate the depressive state.

It is worth noting that the relationship between facial affect recognition and functional outcomes are not universal in the literature, with some studies failing to demonstrate any association between social cognitive performance and psychosocial functioning. For instance, Loi et al. (2013) found no association between body language interpretation and social adaption. Taken together, four of the five studies in the current review suggest a link between social cognition and social performance. However, considering this divergence in results, lack of replication of findings and limitations of the indirect evidence available, the relationship between social cognition and social performance should be considered speculative.

3.1.2. Emotional and empathic performance

While there is very little empirical research on the relationship between social cognition and emotion processing, the response of depressed patients to social stimuli in general has received considerable attention. Depressed individuals have greater difficulty than controls at ignoring the emotional dimension of facial expressions (Gilboa-Schechtman et al., 2004), suggesting increased sensitivity to emotional social cues. People with depression are also more likely than controls to rate facial expressions as untrustworthy (Bayliss et al., 2017) and are more likely to act fearfully – such as through freezing or tensing – in response to affective facial stimuli (Persad and Polivy, 1993). These reactions likely lead to reduced desire for social interaction and reduce the quality of interpersonal relationships, underscoring the need for more research in this domain.

There is evidence to suggest that depressed patients may experience

a reduced level of empathy compared to non-depressed individuals (Cusi et al., 2011; Domes et al., 2016b; Schneider et al., 2012). In fact, the degree of empathy retained whilst acutely depressed may be a protective factor. Greater empathy in depressed patients was associated with improved psychosocial functioning, particularly regarding improved social problem solving (Thoma et al., 2015). A link between empathy and social ability has been identified in the sub-population of depressed mothers, who find it more difficult to correctly identify infant facial emotion (Arteche et al., 2011; Stein et al., 2010) and respond to the infant with fewer comforting behaviours or greater avoidance compared to non-depressed mothers (Macrae et al., 2015).

It also appears that depressed women with greater theory of mind ability are less likely to have dependent or anxious emotional attachment styles (Koelkebeck et al., 2017). This suggests theory of mind may be valuable for higher emotional functioning in daily life, for example through a reduced reliance on others. However, given the limited evidence base currently in this domain, these findings should again be considered preliminary.

3.1.3. General cognitive functioning

Objective and self-perceived cognitive performance are core components of psychosocial function, as both share close ties with occupational or social ability and contribute to subjective feelings of engagement and concentration (Knight and Baune, 2018a). Social cognitive performance in depressed populations also appears connected to general cognitive ability. Impairments in theory of mind (Uekermann et al., 2008b; Zobel et al., 2010) and prosody interpretation (Uekermann et al., 2008a) have been associated with performance difficulties in the cognitive domains of executive functioning and working memory. In particular, these studies identified that deficits with both verbal fluency and inhibition are related to theory of mind, pointing to a mutual negative interaction between social cognition and general cognitive function. Similarly, lower cognitive flexibility was associated with poorer performance in both facial affect recognition and theory of mind (Förster et al., 2018). With working memory, Levens and Gotlib (2010) found depressed participants to be quicker than controls at integrating sad content into a working memory task, but slower at linking more complex emotional stimuli into working memory. Working memory may further be impacted by high levels of suicidality in a depressed population, as Xie et al. (2018) detected an association between suicidal ideations and smaller overall working memory capacity during an emotional face task. In addition, Knight and Baune (2018b) found that poor prosody interpretation was linked with lower self-reported cognitive function in individuals with remitted major depressive disorder.

Notably, some conflicting results have detected no correlations between depressed patients' performances on social cognitive tasks and their neurocognitive functioning (Deveney and Deldin, 2004; Dooze-Grünefeld et al., 2015; Koelkebeck et al., 2017). One study even reported the counter-intuitive result that improved planning ability was associated with poorer facial affect recognition performance in a depressed group (Förster et al., 2018).

3.1.4. General quality of life

Impairments to social cognition also impact on quality of life measures in major depressive disorder. For example, reduced theory of mind performance in depressed patients was associated with a lower *Global Assessment of Functioning* score (Cusi et al., 2013). Conversely, increased recognition accuracy for happy facial expressions was linked with higher self-reporting of personal well-being, social functioning and symptom burden (Tranter et al., 2009). Impaired ability to mentalise is also associated with self-reported difficulties with social adjustment in the work, leisure and family relationship domains of psychosocial functioning (Segal et al., 1993). Finally, Knight and Baune (2018b) demonstrated that prosody interpretation, but not facial affect recognition or meaning interpretation, was associated with distinct

functional deficits in domains of occupational functioning and interpersonal relationships.

In older depressed people, Phillips et al. (2010) found that emotion-labelling ability was a strong predictor of quality of life. However, in an elderly population it must be considered that organic brain diseases (e.g., cerebral small vessel disease) may contribute to impaired emotion-labelling or quality of life independent of depression. Further research on elderly populations is needed to disentangle the effect of social cognition from potential organic confounders.

3.2. Treatment options

A wide variety of treatment modalities have been trialled to target social cognitive dysfunction in depressed patients. These modalities include various pharmacological options (both standard anti-depressants and more novel agents), procedural therapies and the psychotherapies. This section presents the major findings according to specific domain of social cognition.

3.2.1. Facial affect recognition

By far the greatest wealth of information regarding treatment of social cognition can be found in the domain of facial affect recognition. The stimuli used in these studies usually consists of a standardised set of faces depicting the cardinal emotions, such as Ekman and Friesen's (1976) *Pictures of Facial Affect*. There remains some ambiguity as to whether facial affect recognition is itself a measure of theory of mind or an independent concept (Berlim et al., 2012; Szanto et al., 2012). This review considers facial affect recognition to be a simplistic measure of social cognition, while theory of mind is a higher order task typically involving synthesis of a range of social information and will be considered separately.

There is some evidence that the accuracy of interpreting facial expressions improves after effective treatment of depression. Successful trials have been conducted using citalopram (Shiroma et al., 2014; Tranter et al., 2009), reboxetine (Tranter et al., 2009), non-specific anti-depressant pharmacotherapy (Anderson et al., 2011b; Naudin et al., 2014), intra-nasal oxytocin (MacDonald et al., 2013), repetitive transcranial magnetic stimulation (rTMS; Berlin et al., 2012) and transcranial direct current stimulation (tDCS; Brennan et al., 2017). In the only available comparative study, Tranter et al. (2009) found citalopram superior to reboxetine at two weeks for improving accuracy of facial expression interpretation, but there was no difference in outcome by six weeks of treatment.

Other treatments have been effective for improving accuracy in a specific emotional valence: a single dose of oral reboxetine improved positive face recognition (Harmer et al., 2009), while an intravenous infusion of citalopram improved fearful face recognition (Bhagwagar et al., 2004). Recognition of angry faces improved following both a course of ten rTMS treatments (Schutter et al., 2010) and inpatient psychiatric management (Douglas et al., 2011).

There are other treatments that have not yet shown benefit for facial affect recognition performance. For example, pharmacological approaches with sertraline (Victor et al., 2013) or four weeks of inpatient psychotropic management (Gaebel and Wölwer, 1992) were not effective in individual studies. Another study using duloxetine therapy found no facial affect processing differences between depressed and control participants at either baseline assessment or following treatment (Fu et al., 2015). There was also no benefit detected for novel approaches using intravenous ketamine (Shiroma et al., 2015), intranasal insulin (Cha et al., 2017) or omega-3 supplementation (Antypa et al., 2012).

Treatment may also have a role in correcting the underlying negative interpretative bias observed in the processing of affective faces in major depressive disorder. Escitalopram (Zhou et al., 2015) and intranasal oxytocin (Domes et al., 2016a) were both found to be effective at reducing a pre-treatment bias toward negative faces, while responders

to rTMS demonstrated less inhibitory processing against negative faces (Leyman et al., 2011). Surguladze et al. (2004) suggest this relationship could be dose-dependent, as use of high-dose anti-depressants was associated with a reduction in the bias toward labelling expressions as sad. Interestingly, more frequent negative interpretations of neutral facial expressions in a treated depressed population were associated with missed anti-depressant doses (Keeley et al., 2007), suggesting adherence to treatment may be a relevant factor.

Evidence is more equivocal for psychological approaches. There was no impact on overall facial affect recognition performance for depressed patients receiving cognitive-behavioural therapy (CBT; Porter et al., 2016), schema therapy (Porter et al., 2016), cognitive behavioural analysis system of psychotherapy (Klein et al., 2014) or inpatient psychoanalytic-interactional group therapy (Karparova et al., 2005; Suslow et al., 2004). In contrast, use of intensive short-term dynamic psychotherapy did result in a clinically significant improvement in social cognitive performance compared to wait-list controls (Ajilchi et al., 2018). However, in general, psychological approaches may be more suited to addressing the negative interpretative bias. Both mindfulness-based cognitive therapy (de Raedt et al., 2012) and inpatient psychoanalytic-interactional group therapy (Dannowski et al., 2006) reduced the pre-treatment bias toward negative faces. There may even be opportunity to develop psychological approaches to specifically counter this interpretative bias, with one study finding that training depressed students to perceive happiness over sadness in ambiguous facial expressions led to improvements in mood (Penton-Voak et al., 2012).

The use of functional magnetic resonance imaging (fMRI) techniques may assist in identifying prognostic markers for treatment response. The cingulate cortex appears to be one area of particular significance, as clinical response to anti-depressant treatment in depressed populations was predicted by increased baseline activation of the rostral (Opmeer et al., 2016) and right subgenual (Keedwell et al., 2010) anterior cingulate cortex to affective faces. Greater baseline anterior cingulate cortex activity to faces also predicted treatment response to both CBT (Costafreda et al., 2009) and the muscarinic antagonist scopolamine (Furey et al., 2015). As well as having predictive value, increased baseline anterior cingulate activity may disappear following therapy, as was the case for a group of patients treated with sertraline (Victor et al., 2013). Of note, enhanced anterior cingulate responsiveness to affective faces also correlated with a more rapid clinical improvement for both fluoxetine therapy (Chen et al., 2007) and intravenous ketamine (Salvadore et al., 2009). Moreover, there was a correlation between the degree of symptomatic improvement to anti-depressants and level of right subgenual anterior cingulate activity (Keedwell et al., 2009). Such findings suggest there could be an opportunity to target treatment to patients with anterior cingulate hyperactivity.

Another functional area of potential importance is the amygdala. The amygdala has an integral role in emotional processing and is known to be hyperactive in depression, particularly for fearful stimuli (Whalen et al., 2002). There is now a significant body of evidence suggesting that amygdala hyperactivity in response to affective faces improves following treatment of depression, with attenuation observed following use of escitalopram, sertraline, venlafaxine-XR and naturalistic anti-depressant treatment (Redlich et al., 2017; Sheline et al., 2001; Williams et al., 2015). Some treatments have been found to alter amygdala response to only a specific valence of affective face. For example, activation to fearful faces improved with citalopram (Anderson et al., 2011a) and escitalopram (Godlewska et al., 2012), while sad faces responded to fluoxetine (Fu et al., 2004), citalopram (Arnone et al., 2012), sertraline (Victor et al., 2010) and scopolamine (Szczepanik et al., 2016). Activation to negative faces reduced following reboxetine therapy (Ruhé et al., 2012), with the degree of change correlating with symptomatic improvement (Ruhé et al., 2014). Treatment with fluoxetine led to increased functional coupling during sad face processing between the amygdala and other limbic structures,

Table 1
Studies investigating the effect of selective serotonin re-uptake inhibitors (SSRIs) on social cognitive performance in major depressive disorder.

<i>Section 1.1 Fluoxetine</i>					
Author	Method	N [MA ± SD; M:F]	SC Stimulus	MDD Criteria	Results
Chen et al. (2007)	Prospective longitudinal	n = 17 [44.1 ± 8.4; 5M:12F]	PFA	DSM-IV	MDD with increased activation of the anterior cingulate cortex while attending to affective faces demonstrated more rapid clinical improvement after 8 weeks of fluoxetine treatment ($t_{15} = 4.63$, $P < 0.001$).
Chen et al. (2008)	Prospective longitudinal	n = 38 [43.1 ± 7.7; 14M:24F]	PFA	DSM-IV	MDD treated with fluoxetine demonstrated increased coupling between the amygdala and right frontal cortex, cingulate cortex, striatum and thalamus when processing sad faces at 8 weeks compared to HC ($P = 26.89$, $P < 0.001$).
Fu et al. (2004)	Prospective longitudinal	n = 38 [43.0 ± 7.8; 14M:24F]	PFA	DSM-IV	Baseline amplified activation of the left amygdala, ventral striatum and frontoparietal cortex in MDD compared to HC when viewing sad faces was attenuated following 8 weeks of fluoxetine ($t_{18} = 4.75$, $P < 0.001$).
Fu et al. (2007)	Prospective longitudinal	n = 38 [43.0 ± 7.8; 14M:24F]	PFA	DSM-IV	Impaired baseline happy face processing in MDD compared to HC (attenuated activity in limbic-subcortical and extrastriate visual regions) improved significantly following 8 weeks of fluoxetine ($F_{1,36} = 7.0$, $P < 0.02$).
Wang et al. (2012)	Prospective longitudinal	n = 36 [31.6 ± 7.4; 14M:22F]	IAPS	DSM-IV	MDD treated with 8 weeks of fluoxetine did not improve accuracy at interpreting positively-valenced pictures compared to HC. Treated MDD demonstrated attenuated activations of the right insula and left anterior cingulate cortex toward positive stimuli ($t = 3.61$ and $t = 3.04$, $P < 0.005$) and right middle frontal gyrus toward negative stimuli ($t = 4.74$, $P < 0.005$).
<i>Section 1.2 Citalopram</i>					
Author	Method	N [MA ± SD; M:F]	SC Stimulus	MDD Criteria	Results
Anderson et al. (2011a)	Prospective longitudinal	n = 26 [31.6 ± 10.8; 4M:22F]	PFA	DSM-IV	Single administration of IV citalopram in both recovered MDD and HC enhanced left anterior cingulate activity to happy faces ($Z = 3.88$, $P < 0.05$), right lateral orbitofrontal activity to sad faces ($Z = 4.15$, $P < 0.05$) and reduced amygdala activity bilaterally to fearful faces ($Z_r = 2.81$, $Z_l = 2.77$, $P < 0.05$).
Arnone et al. (2012)	Prospective longitudinal	n = 116 [33.9 ± 9.6]	PFA	DSM-IV	Citalopram treatment over 8 weeks normalised amygdala responses bilaterally to sad faces, but not fearful faces, in rMDD patients compared to HC ($Z_r = 3.59$, $P = 0.003$; $Z_l = 3.03$, $P = 0.02$).
Bhagwagar et al. (2004)	DBRCT	n = 40 [37.3 ± 3.7; 0M:40F]	PFA	DSM-IV	rMDD given citalopram infusion demonstrated improved accuracy of fear recognition relative to HC ($F_{1,18} = 5.5$, $P = 0.03$), but not for other expressions.
Shiroma et al. (2014)	Prospective longitudinal	n = 30 [65.3 ± 7.0; 30M:0F]	FEEST	OPCRIT	Facial affect recognition accuracy improved significantly from baseline in older age MDD treated with citalopram for 7 days ($\chi^2 = 34.5$, $P < 0.001$).
Tranter et al. (2009)	Prospective longitudinal	n = 108 [35.5 ± 10.3; 50M:58F]	PFA	MINI	MDD treated with anti-depressant (citalopram or reboxetine) demonstrated significantly improved performance on recognition of happy ($P < 0.05$), surprised ($P < 0.01$) and disgusted faces ($P < 0.001$). Citalopram was superior to reboxetine at 2 weeks ($F_{2,45} = 7.66$, $P = 0.001$), but equal at 6 weeks.
<i>Section 1.3 Escitalopram</i>					
Author	Method	N [MA ± SD; M:F]	SC Stimulus	MDD Criteria	Results
Chen et al. (2014)	Prospective longitudinal	n = 20 [45.7 ± 8.0]	IAPS	DSM-IV	MDD treated with 6 weeks of escitalopram therapy demonstrated no overall change in amygdala activity to emotional stimuli.
Godlewska et al. (2012)	DBRCT	n = 59 [32.2 ± 11.7; 23M:36F]	JACFEE	DSM-IV	MDD treated with 7 days of escitalopram demonstrated normalised amygdala activity in response to fearful faces compared to placebo-treated MDD ($t_{40} = 2.73$, $P < 0.009$).
Jiang et al. (2012)	Prospective longitudinal	n = 21 [29.5 ± 8.0; 9M:12F]	UPD	DSM-IV	First-episode MDD treated with 2–3 months of escitalopram demonstrated changes to fMRI activation across multiple brain regions in response to both sad and happy facial stimuli (various t -tests, $P = 0.000$).
Rosenblau et al. (2012)	Prospective longitudinal	n = 24 [44.7 ± 11.7; 14M:10F]	IAPS	DSM-IV	MDD treated with 8 weeks of escitalopram therapy demonstrated significant improvement of lowered amygdala ($t_{44} = 2.55$, $P_{DOR} = 0.018$) and prefrontal activation (various t -tests, $P < 0.05$) for negative versus neutral affective stimuli compared to HC.
Williams et al. (2015)	OLRCT	n = 114 [32.4 ± 12.4; 58M:56F]	UPD	DSM-IV	Following 8 weeks of anti-depressant therapy (escitalopram, sertraline or venlafaxine-XR), MDD treatment responders demonstrated normalised amygdala responses to happy ($P = 0.031$) and sad ($P = 0.011$) expressions.
Zhou et al. (2015)	Prospective longitudinal	n = 50 [44.5 ± 15.5; 24M:26F]	CFAPS	DSM-IV	Pre-treatment bias towards negative faces in MDD compared to HC ($F_1 = 8.78$, $P = 0.013$) normalised following 8 weeks of escitalopram therapy ($F_1 = 1.35$, $P = 0.30$).

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Table 1 (continued)

Section 1.4 Sertraline					
Author	Method	N [MA ± SD; M:F]	SC Stimulus	MDD Criteria	Results
Sheline et al. (2001)	Prospective longitudinal	n = 22 [40.1; 10M:12F]	PFA	DSM-IV	MDD treated with 8 weeks of sertraline demonstrated a normalised left ($F_{1,10} = 5.74, P < 0.05$) and right ($F_{1,10} = 5.5, P < 0.05$) amygdala activation in response to affective faces compared to HC.
Victor et al. (2010)	Prospective longitudinal	n = 63 [30.1 ± 8.0; 25M:38F]	NSSFE	DSM-IV	MDD treated with 8 weeks of sertraline demonstrated reduced right amygdala responses to sad versus neutral faces compared to HC ($t_{18} = 2.21, P = 0.02$).
Victor et al. (2013)	Prospective longitudinal	n = 20 [30.8 ± 5.4; 7M:13F]	NSSFE	DSM-IV	MDD treated with 8 weeks of sertraline performed no differently to HC on a backwards masking task of facial affect recognition, although MDD following treatment did demonstrate decreased activity in the pregenual anterior cingulate cortex compared to HC ($t_{18} = 3.98, P < 0.001$).
Williams et al. (2015)	OLRCT	n = 114 [32.4 ± 12.4; 58M:56F]	UPD	DSM-IV	Following 8 weeks of anti-depressant therapy (escitalopram, sertraline or venlafaxine-XR), MDD treatment responders demonstrated normalised amygdala responses to happy ($P = 0.031$) and sad ($P = 0.011$) expressions.
Section 1.5 Paroxetine					
Author	Method	N [MA ± SD; M:F]	SC Stimulus	MDD Criteria	Results
Ruhé et al. (2012)	Prospective longitudinal	n = 44 [43.5 ± 8.0; 28M:16F]	PFA	DSM-IV	MDD who responded to reboxetine over a 12-week period demonstrated significantly lower amygdala ($Z = 3.24, P = 0.001$), right dorsolateral pre-frontal cortex ($Z = 3.53, P < 0.001$) and left nucleus accumbens ($Z > 3.28, P < 0.002$) activations compared to non-responders.
Ruhé et al. (2014)	Prospective longitudinal	n = 20 [42.7 ± 8.0; 12M:8F]	PFA	DSM-IV	Symptom improvement in MDD treated with 12 weeks of reboxetine correlated with attenuation of left amygdala activation while attending to negative facial expressions ($r = 0.53, P = 0.041$).
Section 1.6 Non-specific SSRI					
Author	Method	N [MA ± SD; M:F]	SC Stimulus	MDD Criteria	Results
Opmeer et al. (2016)	Prospective longitudinal	n = 81 [38.7 ± 9.8; 32M:49F]	KDEF	DSM-IV	Baseline rostral anterior cingulate cortex activation to happy faces in MDD was predictive of clinical response to SSRI therapy ($t = 4.46, P = 0.026$). Response to treatment led to a decrease in right insula activation when processing happy faces ($t = 5.38, P < 0.001$).
Section 1.7 Augmented SSRI					
Author	Method	N [MA ± SD; M:F]	SC Stimulus	MDD Criteria	Results
Rizvi et al. (2013)	Prospective longitudinal	n = 39 [37.7 ± 10.9; 13M:26F]	IAPS	DSM-IV	MDD who did not respond to 6 weeks of combined fluoxetine/olanzapine therapy rated affective pictures as more aversive compared to responders. High baseline posterior cingulate cortex activity to positive images ($r = 0.59, P = 0.008$) and high baseline premotor cortex activity to negative images ($r = 0.66, P = 0.002$) predicted treatment response at 6 weeks.

Note. CFAPS = Chinese Facial Affective Picture System; DBRCT = Double Blinded Randomised Controlled Trial; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; FEEST = Facial Expressions of Emotion; Stimuli and Tests; fMRI = Functional Magnetic Resonance Imaging; = HC Healthy Controls; IAPS = International Affective Picture System; IV = Intravenous; JACFEE = Japanese and Caucasian Facial Expressions of Emotion; KDEF = Karolinska Directed Emotional Faces; MA ± SD = Participants' Mean Age and Standard Deviation; MDD = Major Depressive Disorder; M:F = Ratio of Male to Female Participants; MINI = Mini-International Neuropsychiatric Interview; N = Number of Participants; NSSFE = NimStim Set of Facial Expressions; OLRCT = Open Label Randomised Controlled Trial; OPCRT = Operational Criteria Diagnostic System; PFA = Ekman and Friesen's Pictures of Facial Affect; rMDD = Remitted Major Depressive Disorder; SC = Social Cognition; SSRI = Selective Serotonin Re-uptake Inhibitor; UPD = University of Pennsylvania Standardised Expression Database.

Table 2
Studies investigating the effect of serotonin and noradrenaline re-uptake inhibitors (SNRIs) on social cognitive performance in major depressive disorder.

Section 2.1 Duloxetine	Author	Method	N [MA ± SD; M:F]	SC Stimulus	MDD Criteria	Results
	Fu et al. (2015)	Prospective longitudinal	n = 57 [39.6 ± 10.7; 31M:26F]	PFA	DSM-IV	No differences in facial affect processing or associated fMRI activity were observed between MDD and HC at baseline or following 8 weeks of duloxetine therapy.
Section 2.2 Venlafaxine	Author	Method	N [MA ± SD; M:F]	SC Stimulus	MDD Criteria	Results
	Davidson et al. (2003)	Prospective longitudinal	n = 17 [35.1 ± 9.6; 8M:9F]	IAPS	DSM-IV	MDD treated with 8 weeks of venlafaxine-IR demonstrated enhanced activation of left anterior cingulate cortex to negative affective stimuli compared to HC ($Z = 4.08$, $P < 0.001$), while MDD with greater left anterior cingulate activation at baseline demonstrated greater treatment response (t not reported).
	Kalin et al. (1997)	Preliminary study	n = 4 [MA and M:F not reported]	IAPS	DSM-IV	MDD treated with 2 weeks of venlafaxine had normalised activation in the right secondary visual cortex for positively-valenced stimuli from baseline compared to HC ($\chi^2_2 = 18.25$, $P < 0.0001$).
	Samson et al. (2011)	Prospective longitudinal	n = 33 [39.5 ± 10.4; 22M:11F]	UPD	DSM-IV	MDD responders to anti-depressant therapy (venlafaxine or mirtazapine) demonstrated improved activation in the left superior parietal region when viewing sad faces after 4 weeks ($t = 3.88$, $P_c = 0.032$). Treatment response also predicted by baseline hyperactivation in right precentral gyrus, left paracentral lobule, visual cortex, left middle temporal gyrus and right caudate nucleus.
	Schaefer et al. (2006)	Prospective longitudinal	n = 23 [31.4 ± 8.7; 7M:16F]	IAPS	DSM-IV	MDD demonstrated a distinctive neural hypo-activity pattern when responding to affective stimuli compared to HC at baseline, which then normalised following venlafaxine therapy (various F -tests, $P < 0.05$).
	Williams et al. (2015)	OLRCT	n = 114 [32.4 ± 12.4; 58M:56F]	UPD	DSM-IV	Following 8 weeks of anti-depressant therapy (escitalopram, sertraline or venlafaxine-XR), MDD treatment responders demonstrated normalised amygdala responses to happy ($P = 0.031$) and sad ($P = 0.011$) expressions.

Note. DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; fMRI = Functional Magnetic Resonance Imaging; HC = Healthy Controls; IAPS = International Affective Picture System; MA ± SD = Participants' Mean Age and Standard Deviation; MDD = Major Depressive Disorder; M:F = Ratio of Male to Female Participants; N = Number of Participants; OLRCT = Open Label Randomised Controlled Trial; PFA = Ekman and Friesen's Pictures of Facial Affect; SC = Social Cognition; UPD = University of Pennsylvania Standardised Expression Database.

Table 3
Studies investigating the effect of other classes of anti-depressants on social cognitive performance in major depressive disorder.

Section 3.1 Noradrenergic and specific serotonergic anti-depressants (NaSSA)					
Author	Method	N [MA \pm SD; M:F]	SC Stimulus	MDD Criteria	Results
Domschke et al. (2016)	Prospective longitudinal	n = 50 [44.2 \pm 14.7; 18M:32F]	IAPS	DSM-IV	MDD treated with 4 weeks of mirtazapine therapy showed improvement of hypoactivation in the right parietal region ($F_{1,28} = 5.8$, $P < 0.05$) compared to HC when viewing affective stimuli, as well as increased activity in the dorsolateral prefrontal cortex bilaterally ($F_{1,26} = 4.9$, $P < 0.05$).
Samson et al. (2011)	Prospective longitudinal	n = 33 [39.5 \pm 10.4; 22M:11F]	UPD	DSM-IV	MDD responders to anti-depressant therapy (mirtazapine or venlafaxine) demonstrated improved activation in the left superior parietal region when viewing sad faces after 4 weeks ($t = 3.88$, $P_e = 0.032$). Treatment response also predicted by baseline hyperactivation in right precentral gyrus, left paracentral lobule, visual cortex, left middle temporal gyrus and right caudate nucleus.
Section 3.2 Selective noradrenergic re-uptake inhibitors (NRIs)					
Author	Method	N [MA \pm SD; M:F]	SC Stimulus	MDD Criteria	Results
Harmer et al. (2009)	DBRCT	n = 64 [37 \pm 12.3; 30M:34F]	PFA	DSM-IV	MDD administered a single dose of oral reboxetine demonstrated significantly improved recognition of positive facial expressions compared to MDD given placebo ($F_{1,31} = 8.4$, $P = 0.007$), but there was no improved recognition of other valences of emotion.
Tranter et al. (2009)	Prospective longitudinal	n = 108 [35.5 \pm 10.3; 50M:58F]	PFA	MINI	MDD treated with anti-depressant (reboxetine or citalopram) demonstrated significantly improved performance on recognition of happy ($P < 0.05$), surprised ($P < 0.01$) and disgusted faces ($P < 0.001$). Citalopram was superior to reboxetine at 2 weeks ($F_{2,45} = 7.66$, $P = 0.001$), but equal at 6 weeks.
Section 3.3 Noradrenaline and dopamine re-uptake inhibitor (NDRI)					
Author	Method	N [MA \pm SD; M:F]	SC Stimulus	MDD Criteria	Results
Robertson et al. (2007)	Prospective longitudinal	n = 10 [41.4 \pm 7.0; 3M:7F]	IAPS	DSM-IV	MDD treated with 8 weeks of bupropion-XL therapy demonstrated a strong correlation between reduced HRSD scores and increased activation of middle frontal gyrus to affective stimuli ($r = -0.95$, $P < 0.01$), as well as correlations between reduced HRSD scores and decreased activations of inferior frontal cortex ($r = 0.93$), anterior cingulate gyrus ($r = 0.92$) and amygdala ($r = 0.84$) to sad stimuli.

Note. DBRCT = Double Blinded Randomised Controlled Trial; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; HC = Healthy Controls; HRSD = Hamilton Rating Scale for Depression; IAPS = International Affective Picture System; MA \pm SD = Participants' Mean Age and Standard Deviation; MDD = Major Depressive Disorder; M:F = Ratio of Male to Female Participants; MINI = Mini-International Neuropsychiatric Interview; N = Number of Participants; PFA = Ekman and Friesen's Pictures of Facial Affect; SC = Social Cognition; UPD = University of Pennsylvania Standardised Expression Database.

Table 4
Studies investigating the effect of naturalistic anti-depressant use on social cognitive performance in major depressive disorder.

Author	Method	N [MA \pm SD; M:F]	SC Stimulus	MDD Criteria	Results
Anderson et al. (2011b)	Cross-sectional	n = 230 [33.1 \pm 10.5; 71M:159F]	PFA	DSM-IV	MDD and rMDD receiving anti-depressant therapy performed equally to HC on facial affect recognition, while unmedicated MDD tended to perform worse than HC.
Douglas et al. (2011)	Prospective longitudinal	n = 118 [38.9 \pm 11.1; 44M:74F]	PFA	DSM-IV	MDD who responded to 6 weeks of general psychiatric treatment demonstrated improved recognition of angry facial expressions compared with treatment non-responders ($F_{2,110} = 4.9, P = 0.009$).
Fales et al. (2009)	Prospective longitudinal	n = 41 [35.1 \pm 8.9; 19M:22F]	Affective faces NOS	DSM-IV	MDD who underwent 8 weeks of mixed anti-depressant therapy demonstrated normalisation of dorsolateral prefrontal cortex activity to fearful faces compared to HC ($F_{1,22} = 6.21, P < 0.02$).
Gaebel and Wölwer (1992)	Prospective longitudinal	n = 59 [33.0; 38M:21F]	PFA	RDC	MDD who underwent 4 weeks of inpatient psychotropic management showed no significant improvement on facial affect recognition compared to HC ($P > 0.1$).
Keedwell et al. (2009)	Prospective longitudinal	n = 12 [49; 6M:6F]	PFA	ICD-10	For MDD treated with mixed anti-depressant therapy, reduced activity in the right subgenual cingulate cortex in response to sad, but not happy, expressions at 12 weeks correlated with response to treatment ($r = 0.863, P < 0.001$).
Keedwell et al. (2010)	Prospective longitudinal	n = 12 [49; 6M:6F]	PFA	ICD-10	MDD response at 12 weeks of anti-depressant treatment was predicted by baseline hyperactivation in right subgenual cingulate cortex to sad stimuli ($r = 0.827, P = 0.001$), while poorer clinical response was predicted by hyperactivation of ventrolateral prefrontal cortex to both happy and sad stimuli (r not reported).
Keeley et al. (2007)	Prospective longitudinal	n = 22 [46.3 \pm 8.6; 8M:14F]	PFA	DSM-IV	Negative interpretation of neutral facial expressions by treated MDD was significantly associated with missed anti-depressant doses ($r = -0.69, P = 0.0004$), while MDD who reported positive or neutral interpretations were associated with improved adherence ($t = 3.7, P = 0.002$).
Naudin et al. (2014)	Prospective longitudinal	n = 63 [33.7 \pm 11.1; 23M:40F]	FEEST	DSM-IV	MDE who responded to anti-depressant therapy showed normalised performance in facial affect recognition compared to HC, particularly with happy faces ($Q = 30.82, P < 0.001$).
Redlich et al. (2017)	Prospective longitudinal	n = 58 [47.0 \pm 9.2; 27M:31F]	PFA	DSM-IV	MDD treated with naturalistic pharmacotherapy demonstrated normalised amygdala activity toward both sad ($Z_r = 3.28, P = 0.001$; $Z_l = 3.06, P = 0.001$) and happy faces ($Z = 2.09, P = 0.018$).
Surguladze et al. (2004)	Cross-sectional	n = 56 [44.9 \pm 11.6; 24M:32F]	FEEST	DSM-IV	Use of high-dose anti-depressant medication in MDD was associated with a response bias away from labelling sad expressions as sad ($t_{26} = 2.2, P < 0.01$), but not for labelling happy expressions as happy.
Wells et al. (2014)	Cross-sectional	n = 94 [33.8 \pm 11.0; M:F not reported]	IAPS	DSM-IV	MDD on anti-depressant therapy demonstrated greater attention to positive affective stimuli and reduced bias toward negative affective stimuli than unmedicated MDD, but performed similarly to HC ($P_s < 0.05$).

Note. DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; FEEST = Facial Expressions of Emotion: Stimuli and Tests; HC = Healthy Controls; IAPS = International Affective Picture System; ICD-10 = International Statistical Classification of Diseases and Related Health Problems, Tenth Revision; MA \pm SD = Participants' Mean Age and Standard Deviation; MDE = Major Depressive Episode; MDD = Major Depressive Disorder; M:F = Ratio of Male to Female Participants; N = Number of Participants; NOS = Not Otherwise Specified; PFA = Ekman and Friesen's Pictures of Facial Affect; RDC = Research Diagnostic Criteria; rMDD = Remitted Major Depressive Disorder; SC = Social Cognition.

Table 5
Studies investigating the effect of non-conventional pharmacotherapeutic approaches on social cognitive performance in major depressive disorder.

Section 5.1 Intravenous ketamine					
Author	Method	N [MA ± SD; M:F]	SC Stimulus	MDD Criteria	Results
Murrough et al. (2015)	Prospective longitudinal	n = 38 [36.5 ± 11.5; 21M:17F]	PFA	DSM-IV	Treatment-resistant MDD given a single dose of IV ketamine demonstrated normalisation of neural activity in the right caudate when viewing positive facial affect ($k > 574$, $P_{FWE} < 0.05$).
Salvadore et al. (2009)	Prospective longitudinal	n = 22 [39.9 ± 14.6; 14M:8F]	NSSFE	DSM-IV	Increased anterior cingulate cortex activity to fearful faces at baseline was correlated with anti-depressant response to IV ketamine in MDD ($r_2 = 0.68$, $P < 0.05$).
Shiroma et al. (2015)	Prospective longitudinal	n = 15 [52; 15M:0F]	FEEST	DSM-IV	No effect on facial affect recognition performance in treatment-resistant MDD following 6 infusions of IV ketamine over a 12-day period.
Section 5.2 Intranasal oxytocin					
Author	Method	N [MA ± SD; M:F]	SC Stimulus	MDD Criteria	Results
Domes et al. (2016a)	DBRCT	n = 43 [46.9 ± 10.1; 18M:25F]	KDEF	ICD-10	Single dose of intra-nasal oxytocin in MDD reduced attention toward angry facial expressions ($F_{2,82} = 3.20$, $P < 0.05$) and increased attention to happy faces with prolonged exposure ($F_{2,82} = 3.21$, $P < 0.05$).
MacDonald et al. (2013)	DBRCT	n = 18 [43.7 ± 12.2; 18M:0F]	RMET	MINI	Intra-nasal oxytocin improved facial affect recognition performance in male MDD compared to placebo ($F_{1,16} = 4.67$, $P < 0.05$).
Section 5.3 Intravenous erythropoietin					
Author	Method	N [MA ± SD; M:F]	SC Stimulus	MDD Criteria	Results
Miskowiak et al. (2009)	DBRCT	n = 17 [34.5 ± 10.4; 11M:6F]	IAPS	DSM-IV	MDD administered IV erythropoietin had significantly reduced false recollections of affective images compared to placebo group ($t = -3.29$, $P = 0.005$).
Miskowiak et al. (2010)	DBRCT	n = 19 [34.3 ± 10.4; 12M:7F]	IAPS	DSM-IV	Single IV erythropoietin dose to MDD was associated with reduction in fear recognition compared to placebo, particularly at higher intensities of emotion ($F_{1,17} = 5.56$, $P < 0.05$).
Section 5.4 Intranasal insulin					
Author	Method	N [MA ± SD; M:F]	SC Stimulus	MDD Criteria	Results
Cha et al. (2017)	DBRCT	n = 35 [47.1 ± 9.9; 13M:22F]	ERT (CANTAB)	DSM-IV	MDD treated with 4 weeks of QID intranasal insulin did not demonstrate any difference in emotion recognition performance compared to placebo.
Section 5.5 Mineralocorticoid receptor blockade					
Author	Method	N [MA ± SD; M:F]	SC Stimulus	MDD Criteria	Results
Wingenfeld et al. (2016)	DBRCT	n = 35 [47.1 ± 9.9; 13M:22F]	MET, MASC	DSM-IV	Spironolactone use in MDD had no effect of emotional empathy compared to HC, but its use decreased cognitive empathy scores in MDD compared to HC ($F_{1,67} = 7.60$, $P = 0.008$).
Section 5.6 Muscarinic antagonist					
Author	Method	N [MA ± SD; M:F]	SC Stimulus	MDD Criteria	Results
Furey et al. (2013)	DBRCT	n = 36 [31.5 ± 8.2; 23M:13F]	KDEF	DSM-IV	The magnitude of treatment response for MDD treated with scopolamine correlated with increased activity in right and left middle occipital cortices during emotional face encoding ($r_R = -0.77$, $r_L = -0.85$, $P < 0.005$) and testing ($r_R = -0.81$, $r_L = -0.87$, $P < 0.005$).
Furey et al. (2015)	DBRCT	n = 31 [32.4 ± 8.0; 9M:22F]	FEEST, KDEF, NSSFE	DSM-IV	MDD with greater baseline subgenual anterior cingulate cortex activity to happy faces correlated with improved response to scopolamine ($P < 0.025$), while greater baseline middle occipital cortex activity to sad faces correlated with improved response ($P < 0.025$).

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Table 5 (continued)

Section 5.6 Muscarinic antagonist		Method		N [MA ± SD; M:F]		SC Stimulus	MDD Criteria	Results
Author								
Szczepanik et al. (2016)	DBRCT			n = 29 [31.8 ± 8.5; 9M:20F]		FEEST, KDEF, NSSFE	DSM-IV	MDD did not demonstrate increased accuracy on facial affect recognition following scopolamine use, but left amygdala response to sad faces normalised in treatment responders ($r = -0.72$, $P = 0.004$).
Section 5.7 Omega-3 fatty acid supplementation		Method		N [MA ± SD; M:F]		SC Stimulus	MDD Criteria	Results
Author								
Antypa et al. (2012)	DBRCT			n = 71 [24.7 ± 9.4; 13M:58F]		PFA	MINI	Omega-3 supplementation in rMDD provided no benefit compared to placebo for facial affect recognition performance.

Note. DBRCT = Double Blinded Randomised Controlled Trial; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; ERT = (CANTAB) Emotion Recognition Task from Cambridge Neuropsychological Test Automated Battery; FEEST = Facial Expressions of Emotion: Stimuli and Tests; HC = Healthy Controls; IAPS = International Affective Picture System; ICD-10 = International Statistical Classification of Diseases and Related Health Problems, Tenth Revision; IV = Intravenous; KDEF = Karolinska Directed Emotional Faces; MA ± SD = Participants' Mean Age and Standard Deviation; MASC = Movie for the Assessment of Social Cognition; MET = Multifaceted Empathy Test; MDD = Major Depressive Disorder; M:F = Ratio of Male to Female Participants; MINI = Mini-International Neuropsychiatric Interview; N = Number of Participants; NSSFE = NimStim Set of Facial Expressions; PFA = Ekman and Friesen's Pictures of Facial Affect; QID = *Quater In Die* (Four Times Per Day); RMET = Reading the Mind in the Eyes Task; rMDD = Remitted Major Depressive Disorder; SC = Social Cognition.

such as the right frontal cortex, cingulate cortex, striatum and thalamus (Chen et al., 2008). Additionally, the actions of psychotropics may target various other neural areas of interest, as outlined in Tables 1–5 (Fales et al., 2009; Fu et al., 2007; Furey et al., 2013; Jiang et al., 2012; Murrough et al., 2015; Samson et al., 2011).

Redlich et al. (2017) evaluated amygdala reactivity in response to sad faces following either twelve sessions of ECT or pharmacotherapy. Both treatment conditions attenuated amygdala activity in response to sad faces, suggesting a shared neurobiological mechanism for ECT and pharmacotherapy on facial affect interpretations in MDD. In a similar study by Miskowiak et al. (2017), the authors found that a single session of ECT had no effect on amygdala reactivity in response to emotional faces, suggesting that multiple ECT sessions are required to exert an effect on social cognitive biases (Tables 6 and 7).

Psychological strategies may also help ameliorate amygdala activity, with some evidence supporting both CBT (Fu et al., 2008) and cognitive behavioural analysis system of psychotherapy (Klein et al., 2014). A novel technique using real-time functional magnetic resonance imaging neurofeedback training was successful at normalising amygdala responses toward affective facial stimuli (Young et al., 2017).

Notably, very few of the above treatment studies employed a randomised, clinically controlled design with a longitudinal no-treatment control group. Accordingly, the effect of treatment strategies on MDD cannot be disentangled from the natural course of illness. At present, evidence for a treatment effect should therefore be considered preliminary and indicates the need for controlled studies in this domain.

3.2.2. Affective scenes

Another popular target of social cognitive testing is interpretation of affective pictures from standardised databases, such as the *International Affective Picture System* (Lang et al., 1997). This task includes stimuli ranging from everyday objects or scenes to more intensely emotive scenes, including extremes such as erotica or mutilated bodies.

There is some emerging evidence that anti-depressant medication improves behavioural performance on affective picture tasks. Wells et al. (2014) used a naturalistic sample of depressed patients taking anti-depressant medication and observed a reduced negative interpretative bias compared to a group of unmedicated depressed patients. Similarly, Rizvi et al. (2013) found that treatment non-responders rated affective pictures as more aversive compared to those who responded to therapy. Furthermore, the patients taking medication performed similarly to non-depressed controls when interpreting affective scenes. In contrast, Wang et al. (2012) found no improvement of accuracy in interpreting positively valenced pictures for depressed patients compared to controls after eight weeks of fluoxetine.

One novel approach with some promising early results is intravenous erythropoietin. A single dose was associated with reduced propensity to interpret fearful stimuli (Miskowiak et al., 2010) and a significantly reduced rate of false recollections of affective images presented (Miskowiak et al., 2009). Nevertheless, additional research is needed to gauge the utility of erythropoietin on a wider scale.

Use of fMRI techniques may again be useful in identifying activation patterns that indicate likelihood of response to treatment. One study employing combined fluoxetine/olanzapine therapy found that response to treatment at six weeks could be predicted by high baseline posterior cingulate cortex activity to positive images and high baseline pre-motor cortex activity to negative images (Rizvi et al., 2013).

Multiple other studies using fMRI have demonstrated activation changes post treatment, suggesting biological mechanisms by which anti-depressants act to normalise the processing of affective stimuli. This is particularly noted for viewing negatively valenced stimuli: a course of fluoxetine was associated with increased activations of the right middle frontal gyrus (Wang et al., 2012), escitalopram with attenuation in the amygdala (Rosenblau et al., 2012), venlafaxine-IR with enhanced activation of the left insular and left anterior cingulate cortex (Davidson et al., 2003) and bupropion-XL with decreased activations

Table 6
Studies investigating the effect of procedural therapies on social cognitive performance in major depressive disorder.

Section 6.1 Electro-convulsive therapy (ECT)					
Author	Method	N [MA ± SD; M:F]	SC Stimulus	MDD Criteria	Results
Christ et al. (2008)	Prospective longitudinal	n = 20 [53.1 ± 10.8; 10M:10F]	Sine tones, syllables	DSM-IV	MDD treated with course of ECT demonstrated partial improvement of fMRI activation patterns during processing of auditory stimuli ($P_s < 0.05$).
Redlich et al. (2017)	Prospective longitudinal	n = 58 [47.0 ± 9.2; 27M:31F]	PFA	DSM-IV	MDD treated with course of ECT demonstrated decreased amygdala activity toward sad faces ($z = 2.26$, $P = 0.012$), which also correlated with symptomatic improvement ($r = -0.48$, $P < 0.05$).
Miskowiak et al. (2017)	Prospective longitudinal	n = 27 [39.3; 17M:10F]	ETB	Unclear	Single session of ECT in MDD had no effect on facial affect recognition or to amygdala responses while processing faces.
Zwanzger et al. (2016)	Prospective longitudinal	n = 40 [52.1 ± 11.7; 22M:18F]	IAPS	DSM-IV	A 4-week course of ECT led to normalisation of bilateral parietal hypoactivation on MEG for MDD compared to HC during processing of affective stimuli ($F_{1,36} = 14.34$, $P = 0.001$).
Section 6.2 Repetitive transcranial magnetic stimulation (rTMS)					
Author	Method	N [MA ± SD; M:F]	SC Stimulus	MDD Criteria	Results
Berlim et al. (2012)	Prospective longitudinal	n = 14 [47.6 ± 8.4; 6M:8F]	RMET	HRSD	MDD demonstrated a significant interaction between improved facial affect recognition and symptomatic improvement following a 4-week course of daily rTMS ($F_{1,12} = 7.26$, $P = 0.019$).
Boggio et al. (2007)	DBRCT	n = 26 [48.7 ± 7.9; 8M:18F]	Affective pictures	DSM-IV	A single session of rTMS led to improved performance for MDD on an affective go-no-go task compared to sham therapy ($F = 5.67$, $P = 0.01$).
Leyman et al. (2011)	Prospective longitudinal	n = 14 [44.3 ± 7.6; 4M:10F]	NOS	DSM-IV	MDD responders to 10 days of rTMS demonstrated significant improvements in the inhibitory processing of negatively valenced information ($Z = 1.60$, $P = 0.05$).
Schutter et al. (2010)	Prospective longitudinal	n = 28 [45 ± 12.5; 12M:16F]	MERT	DSM-IV	MDD treated with 10 sessions of rTMS demonstrated significantly improved recognition of angry facial expressions compared to sham therapy ($F_{1,27} = 5.76$, $P = 0.02$), but not with happy faces.
Section 6.3 Transcranial direct current stimulation (tDCS)					
Author	Method	N [MA ± SD; M:F]	SC Stimulus	MDD Criteria	Results
Brennan et al. (2017)	SBRCT	n = 37 [33.1 ± 8.2; 71M:159F]	MERT	ICD-10	tDCS treatment was associated with significantly improved facial affect recognition compared to sham treatment for both MDD and HC ($F_{1,35} = 5.70$, $P = 0.02$).
Section 6.4 Deep brain stimulation (DBS)					
Author	Method	N [MA ± SD; M:F]	SC Stimulus	MDD Criteria	Results
Merkel et al. (2016)	Prospective longitudinal	n = 27 [48.3 ± 20.4; 14M:13F]	MET	DSM-IV	Treatment-resistant MDD receiving 6 months of DBS to the subgenual anterior cingulate cortex experienced a significant reduction of negative bias in their empathic responses ($U = 8.50$, $P = 0.043$).
Section 6.5 Psychosurgery					
Author	Method	N [MA ± SD; M:F]	SC Stimulus	MDD Criteria	Results
Ridout et al. (2007)	Cross-sectional	n = 48 [41.9 ± 7.3; 11M:37F]	TASIT	ICD-10	Treatment-resistant MDD who had received anterior cingulotomy and anterior capsulotomy had reduced accuracy of emotion recognition compared to MDD controls and HC ($F_{2,44} = 3.4$, $P < 0.05$).

Note. DBRCT = Double Blinded Randomised Controlled Trial; DBS = Deep Brain Stimulation; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; ECT = Electro-Convulsive Therapy; ETB = Emotional Test Battery; fMRI = Functional Magnetic Resonance Imaging; HC = Healthy Controls; HRSD = Hamilton Rating Scale for Depression; IAPS = International Affective Picture System; ICD-10 = International Statistical Classification of Diseases and Related Health Problems, Tenth Revision; KDEF = Karolinska Directed Emotional Faces; MA ± SD = Participants' Mean Age and Standard Deviation; MDD = Major Depressive Disorder; MEG = Magnetoencephalography; MERT = Montagne Emotion Recognition Task; MET = Multifaceted Empathy Test; M:F = Ratio of Male to Female Participants; N = Number of Participants; NOS = Not Otherwise Specified; PFA = Ekman and Friesen's Pictures of Facial Affect; RMET = Reading the Mind in the Eyes Task; rTMS = Repetitive Transcranial Magnetic Stimulation; SBRCT = Single Blinded Randomised Controlled Trial; SC = Social Cognition; TASIT = The Awareness of Social Inference Test; tDCS = Transcranial Direct Current Stimulation.

Table 7
Studies investigating the effect of psychotherapeutic approaches on social cognitive performance in major depressive disorder.

Section 7.1 Cognitive-behavioural therapy (CBT)					
Author	Method	N [MA ± SD; M:F]	SC Stimulus	MDD Criteria	Results
Costafreda et al. (2009)	Prospective longitudinal	n = 16 [40.0 ± 9.4; 3M:13F]	PFA	DSM-IV	The fMRI activation response in MDD toward sad faces at baseline could be a predictor of treatment response to CBT ($P = 0.029$).
Fu et al. (2008)	Prospective longitudinal	n = 32 [39.6 ± 9.4; 6M:26F]	PFA	DSM-IV	MDD who underwent 16 sessions of CBT experienced a normalisation of amygdala-hippocampal activity compared to HC ($F_{1,15} = 7.04, P < 0.02$).
Porter et al. (2016)	Prospective longitudinal	n = 127 [38.9 ± 12.3; 42M:85F]	PFA	DSM-IV	Emotional processing performance in MDD did not change following 16 weeks of CBT or schema therapy.
Ritchey et al. (2011)	Prospective longitudinal	n = 36 [35.5 ± 9.0; 14M:22F]	IAPS	DSM-IV	There was no improvement in SC performance following CBT, although MDD compared to HC demonstrated increased prefrontal cortex activation and increased arousal of the amygdala, caudate and hippocampus ($P < 0.005$).
Section 7.2 Mindfulness-based cognitive therapy (mbCT)					
Author	Method	N [MA ± SD; M:F]	SC Stimulus	MDD Criteria	Results
de Raedt et al. (2012)	Prospective longitudinal	n = 71 [45.1 ± 9.4; 19M:52F]	KDEF	DSM-IV	MDD receiving 8 weeks of mbCT demonstrated significantly reduced attentional bias towards negative faces ($t = 1.64, P = 0.05$) and a trend towards reduced attentional bias away from positive faces compared to HC ($t = 1.35, P = 0.09$).
Section 7.3 Cognitive behavioural analysis system of psychotherapy (CBASP)					
Author	Method	N [MA ± SD; M:F]	SC Stimulus	MDD Criteria	Results
Klein et al. (2014)	Prospective longitudinal	n = 20 [38.7 ± 13.9; 8M:12F]	Novel dynamic faces	DSM-IV	MDD following a course of CBASP demonstrated no improvement at identifying the level of emotional intensity in facial affect, although there was evidence of improved left amygdala reactivity on fMRI ($F_{1,18} = 25.32, P < 0.05$).
Section 7.4 Schema therapy					
Author	Method	N [MA ± SD; M:F]	SC Stimulus	MDD Criteria	Results
Porter et al. (2016)	Prospective longitudinal	n = 127 [38.9 ± 12.3; 42M:85F]	PFA	DSM-IV	Emotional processing performance in MDD did not change following 16 weeks of schema therapy or CBT.
Section 7.5 Behavioural activation (BA)					
Author	Method	N [MA ± SD; M:F]	SC Stimulus	MDD Criteria	Results
Shiota et al. (2017)	Prospective longitudinal	n = 59 [18.2 ± 0.4; 40M:19F]	Novel ToM task	CIDI	MDD following BA treatment demonstrated improved dorsomedial prefrontal cortex activity during a ToM task ($t = 3.24, P = 0.016$).
Section 7.6 Inpatient psychoanalytic-interactive group therapy					
Author	Method	N [MA ± SD; M:F]	SC Stimulus	MDD Criteria	Results
Dannowski et al. (2006)	Prospective longitudinal	n = 41 [32.3 ± 8.9; 14M:27F]	UPD	DSM-IV	MDD following inpatient therapy demonstrated a reduction in negative interpretive bias when interpreting sad facial affect ($Z = -3.04, P = 0.002$).
Donges et al. (2005)	Prospective longitudinal	n = 44 [32.1 ± 8.6; 14M:30F]	LEAS	DSM-IV	MDD following inpatient therapy demonstrated a significant increase in ToM performance ($F_{1,42} = 5.6, P < 0.05$), although this did not reach the performance level of HC.
Karparova et al. (2005)	Prospective longitudinal	n = 30 [36.6 ± 10.2; 8M:22F]	Novel schematic faces	DSM-IV	There was no significant change in facial affect processing in MDD following inpatient therapy, despite improvement in depressive symptom severity.
Suslow et al. (2004)	Prospective longitudinal	n = 44 [32.1 ± 8.7; 14M:30F]	Novel schematic faces	DSM-IV	There were no significant improvements in facial affect processing performance for MDD following inpatient therapy.

(continued on next page)

Table 7 (continued)

Section 7.7 Intensive short-term dynamic psychotherapy					
Author	Method	N [MA \pm SD; M:F]	SC stimulus	MDD criteria	Results
Ajlchi et al. (2018)	OLRCT (pilot study)	n = 32 [22; 9M:23F]	RMET	DSM-IV, BDI-II	MDD receiving intensive short-term dynamic therapy demonstrated significant improvement in total social cognition score compared to wait-list controls ($F_{1,28} = 48.31, P < 0.01$).
Section 7.8 Emotion perception training					
Author	Method	N [MA \pm SD; M:F]	SC stimulus	MDD criteria	Results
Penton-Voak et al. (2012)	DBRCT	n = 80 [21 (median); 25M:55F]	KDEF	BDI-II	Depressed students receiving emotion perception training to perceive happiness over sadness in ambiguous facial expressions led to mood improvements ($P = 0.032$).
Smith et al. (2018)	OLRCT	n = 44 [19.3 \pm 2.1; 11M:33F]	WSAP-H; IBQ	MINI	MDD receiving interpretation bias modification demonstrated fewer hostile interpretations of ambiguous social situations ($W_{1,40} = 39.54, P < 0.001$).
Section 7.9 Real-time functional magnetic resonance imaging neurofeedback training (rtfMRIInf)					
Author	Method	N [MA \pm SD; M:F]	SC stimulus	MDD criteria	Results
Young et al. (2017)	DBRCT	n = 34 [31.5 \pm 10.7; 10M:24F]	PFA	DSM-IV	MDD receiving rtfMRIInf training showed decreased amygdala responses to sad faces and increased responses to happy faces following treatment ($t_{33} = 4.01, P < 0.001$).

Note. BA = Behavioural Activation; BDI-II = Beck Depression Inventory-II; CBASP = Cognitive Behavioural Analysis System of Psychotherapy; CBT = Cognitive-Behavioural Therapy; CIDI = World Health Organization World Mental Health Composite International Diagnostic Interview; DBRCT = Double Blinded Randomised Controlled Trial; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; fMRI = Functional Magnetic Resonance Imaging; HC = Healthy Controls; IAPS = International Affective Picture System; IBQ = Interpretation Bias Questionnaire; KDEF = Karolinska Directed Emotional Faces; LEAS = Levels of Emotional Awareness Scale; MA \pm SD = Participants' Mean Age and Standard Deviation; mbCT = Mindfulness-based Cognitive Therapy; MINI = Mini-International Neuropsychiatric Interview; MDD = Major Depressive Disorder; M:F = Ratio of Male to Female Participants; N = Number of Participants; OLRCT = Open Label Randomised Controlled Trial; PFA = Ekman and Friesen's Pictures of Facial Affect; RMET = Reading the Mind in the Eyes Task; rtfMRIInf = Real-Time Functional Magnetic Resonance Imaging Neurofeedback; SC = Social Cognition; ToM = Theory of Mind; UPD = University of Pennsylvania Standardised Expression Database; WSAP-H = Word Sentence Association Paradigm – Hostility.

of the right inferior frontal cortex, right anterior cingulate gyrus and right amygdala (Robertson et al., 2007).

Specific brain activations to positively valenced affective stimuli have also been observed to normalise following treatment. Depressed patients treated with fluoxetine showed decreased activation in the right insula and left anterior cingulate cortex (Wang et al., 2012), while those treated with venlafaxine had normalised activation in the right secondary visual cortex for positively valenced stimuli (Kalin et al., 1997). Additionally, treatment may reduce attentional bias toward negative stimuli, as patients receiving anti-depressant medication were found to be more attentive to positive affective stimuli following treatment (Wells et al., 2014).

Other studies have detected neural changes following treatment that were independent of the emotional valence of the stimuli. Mirtazapine therapy was associated with attenuated right parietal region hypoactivation and increased bilateral dorsolateral prefrontal cortex activity in depressed compared to non-depressed subjects (Domschke et al., 2016). Schaefer et al. (2006) found that depressed patients demonstrated widespread neural hypoactivity at baseline across the pre-frontal cortex, hippocampus, insula, basal ganglia and temporal and parietal cortices. This pattern normalised following venlafaxine therapy. Clinical improvement with bupropion-XL was associated with increased activation of the middle frontal gyrus to affective stimuli (Robertson et al., 2007). However, Chen et al. (2014) found no overall change to amygdala activity when viewing emotional stimuli following six weeks of escitalopram therapy.

There is limited support for the use of procedural therapies, with Boggio et al. (2007) showing that depressed patients receiving a single session of rTMS had improved performance on an affective go-no-go task compared to sham therapy. A separate study looking at a four-week course of electro-convulsive therapy (ECT) found no improvement for depressed subjects compared to controls at interpreting affective stimuli, although bilateral parietal hypoactivation on magnetoencephalography normalised following treatment (Zwanzger et al., 2016).

Limited data are available regarding psychological therapies in this area. Ritchey et al. (2011) found no overall improvement in depressed patients' ability to interpret affective pictures compared to controls following a course of CBT. However, following therapy, depressed patients exhibited increased activation of multiple brain regions involved in the processing of emotionally salient information, including the pre-frontal cortex, amygdala, caudate and hippocampus.

3.2.3. Theory of mind

Another potential target of treatment is theory of mind, defined as the capacity to infer the thoughts, intentions and feelings of others. Treatments targeted in this area have predominantly been psychological or procedural.

Inpatient psychoanalytic-interactional group therapy over an average period of seven weeks improved the performance of depressed patients on a task relating to mentalisation from both the self and other perspectives (Donges et al., 2005). Despite this improvement following treatment, the depressed group still did not reach the performance level of non-depressed controls. Another study by Shiota et al. (2017) considered behavioural activation strategies in a mildly depressed population, finding improved reaction times and increased activation in the dorsomedial pre-frontal cortex when attending to positively valenced stimuli on a similar task relating to self and other mentalisation. Smith et al. (2018) evaluated a computerised interpretation bias training programme, which involved training participants to consider neutral or positive explanations for ambiguous social scenarios. Relative to a control condition, the bias modification programme resulted in greater reductions in hostile social interpretations and increased benign interpretations. However, these advantages did not extend to depressive interpretation biases (e.g., pessimism), suggesting that bias modification may be more effective in reducing anger/hostility than low mood.

Regarding procedural therapies, Merkl et al. (2016) gave treatment-resistant depressed subjects six months of deep brain stimulation in the subgenual anterior cingulate cortex and found that these patients experienced a significant reduction of negative bias in their empathic responses compared to controls. Ridout et al. (2007) had previously demonstrated that treatment-resistant depressed patients with pre-existing anterior cingulotomy and anterior capsulotomy had significantly impaired theory of mind performance to both depressed patients without psychosurgery and non-depressed controls. Thus, this region appears to have an important mechanistic role and may be an important target for treatment.

The single available pharmacological study considered the utility of mineralocorticoid receptor blockade (using spironolactone) on theory of mind, but use of this agent in depressed patients had no effect of emotional empathy compared to controls, although did decrease cognitive empathy scores on one measure (Wingenfeld et al., 2016).

3.2.4. Auditory/prosodic stimuli

Very limited evidence is available to assess the role of interventions addressing social cognitive deficits in the interpretation of prosody in major depressive disorder, although one study has investigated the impact of ECT. Christ et al. (2008) found that depressed patients had significantly improved performance interpreting affective prosody following a course of ECT. This remains an area in need of additional research to both confirm the generalisability of these findings and explore whether other treatment modalities may also play a role in correcting dysfunction in prosody interpretation in depressed populations.

4. Discussion

In major depressive disorder, impaired social cognitive performance is associated with poor psychosocial functioning in domains of general cognitive functioning and quality of life. These difficulties may be mediated through processes such as mentalisation, verbal communication, interpersonal interaction and the key cognitive skills of executive functioning and memory. Considerably less research exists on the link between social cognitive abilities and either social performance or emotional/empathic ability. With only indirect evidence available in these domains, the effect of social cognition in social and emotional performance remains speculative. While general cognition may play a broader role in functioning, the available literature suggests that social cognitive impairments are clinically significant and contribute to the burden of disease in major depressive disorder.

Many existing treatments for major depressive disorder are found to also improve social cognition. This implies that social cognitive deficits share common aetiological antecedents with the targets of current biological and psychological interventions. Certain medications, psychotherapy modalities and procedural interventions appear to increase accuracy in interpreting social information and reduce underlying negative interpretative bias. There is also an emerging body of work suggesting a normalising effect of treatments at a neural level. While psychological therapies promote distinct behavioural and cognitive changes, these may be partially mediated by underlying neurobiological change. In fact, current data suggests psychotropic and psychological therapies engage in shared mechanisms of action, as both treatment modalities appear to affect neurobiological and psychological components of social cognitive function. These findings align with previous work (DeRubeis et al., 2008; Kennedy et al., 2007), which identified substantial overlap in the underlying neurobiological mechanisms of selective serotonin reuptake inhibitors and CBT in the treatment of MDD.

Anti-depressants, in particular citalopram and reboxetine, appear to improve performance on facial affect recognition tasks and, to a lesser extent, for tasks involving interpretation of affective pictures. These effects are mediated through activity within specific neurohormonal pathways, notably within the limbic system. Areas of particular

potential include the anterior cingulate cortex and amygdala, which is unsurprising given the established role these structures have in emotional processing. Medications targeting these areas may develop into specific treatments for social cognitive deficits, while more invasive therapies such as deep brain stimulation may eventually also have a role.

In contrast, a psychotherapeutic approach was generally better suited for treating theory of mind deficits and negative interpretative bias, with only limited benefit in improving overall accuracy rates. Intensive inpatient therapy and behavioural activation in particular were efficacious, while there is a theoretical basis for the use of cognitive and mentalisation-based approaches as well.

Much scarcer data is available for other treatments. ECT may have a role in the interpretation of prosody in major depressive disorder, while patients who receive rTMS and tDCS have shown improved facial affect recognition in single research studies. However, it is unclear whether improvements following these procedural interventions are closely associated with or independent of general clinical improvement (Berlim et al., 2012). This area of investigation is very much in its infancy and needs replication in larger trials, in which treatment of social cognitive deficits are considered a primary clinical outcome. Likewise, clinical trials of psychological interventions for social cognitive deficits in MDD are warranted.

The findings of the present review highlight important prognostic markers that could become valuable indicators of treatment response for social cognitive deficits or the associated psychosocial dysfunction. In particular, the fMRI findings suggest important roles of the anterior cingulate cortex and amygdala. Overactivity in these regions may signal hypersensitivity to facial affect, which primarily manifests as increased perception of negative emotions (e.g. fear, anger) in depressed individuals. Given that hypersensitivity to negative facial affect appears associated with reduced social performance, social isolation and reduced empathy, it is hypothesised that activity in these regions could become a prognostic aid in gauging the severity of psychosocial deficits and predict the potential benefit of targeting underlying social cognitive distortions in the interpretation of facial affect.

Many current treatments for depression appear to have a role in the treatment of social cognitive deficits and the associated psychosocial functional impairments. Future developments in personalised medicine could potentially identify neural patterns that either indicate the use of a particular treatment or provide prognostic information about the likelihood of response to intervention. The impact and treatment of social cognitive deficits in major depressive disorder remains an important emerging field for future research.

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