Electrophysiological and neurocognitive correlates of self-blame and associated vulnerability to major depression

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School of Psychological Sciences
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<tbody>
<tr>
<td>AMDP</td>
<td>a symptom rating interview translated from German</td>
</tr>
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<td>AMT</td>
<td>Autobiographical Memory Test</td>
</tr>
<tr>
<td>ANOVA</td>
<td>analysis of variance</td>
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<tr>
<td>BA</td>
<td>Brodmann area</td>
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<td>BOLD</td>
<td>blood-oxygen-level dependent</td>
</tr>
<tr>
<td>dIPFC</td>
<td>dorsolateral prefrontal cortex</td>
</tr>
<tr>
<td>DSM-IV</td>
<td>diagnostic and statistical manual of mental disorders, 4th edition</td>
</tr>
<tr>
<td>EEG</td>
<td>electroencephalography</td>
</tr>
<tr>
<td>EFEC</td>
<td>event-feature-emotion complex</td>
</tr>
<tr>
<td>ELS</td>
<td>early life stress</td>
</tr>
<tr>
<td>fMRI</td>
<td>functional magnetic resonance imaging</td>
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<tr>
<td>FWE</td>
<td>family-wise error</td>
</tr>
<tr>
<td>GAF</td>
<td>global assessment of functioning</td>
</tr>
<tr>
<td>GFP</td>
<td>global field power</td>
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<tr>
<td>GLM</td>
<td>general linear model</td>
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<tr>
<td>HC</td>
<td>healthy control</td>
</tr>
<tr>
<td>ICD-10</td>
<td>International Classification of Diseases</td>
</tr>
<tr>
<td>LIFE</td>
<td>Longitudinal Interval Follow-up Evaluation</td>
</tr>
<tr>
<td>MADRS</td>
<td>Montgomery-Åsberg Depression Rating Scale</td>
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<tr>
<td>MDD</td>
<td>major depressive disorder</td>
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<td>MDE</td>
<td>major depressive episode</td>
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<tr>
<td>OGM</td>
<td>overgeneralisation of autobiographical memories</td>
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<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>PPI</td>
<td>psychophysiological interaction</td>
</tr>
<tr>
<td>rACC</td>
<td>rostral anterior cingulate cortex</td>
</tr>
<tr>
<td>rMDD</td>
<td>remitted major depressive disorder</td>
</tr>
<tr>
<td>ROI</td>
<td>region of interest</td>
</tr>
<tr>
<td>SCID-I</td>
<td>structured clinical interview-I for DSM-IV</td>
</tr>
<tr>
<td>SCSR</td>
<td>subgenual cingulate and septal region</td>
</tr>
<tr>
<td>sgACC</td>
<td>subgenual cingulate cortex</td>
</tr>
<tr>
<td>SPM</td>
<td>Statistical Parametic Mapping</td>
</tr>
<tr>
<td>vmPFC</td>
<td>ventromedial prefrontal cortex</td>
</tr>
<tr>
<td>VMST</td>
<td>value-related moral sentiments task</td>
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Abstract

Electrophysiological and neurocognitive correlates of self-blame and associated vulnerability to major depression

Jennifer Ann Gethin, The University of Manchester

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For many, the course of major depressive disorder (MDD) is recurrent, with periods of remission between major depressive episodes (MDEs); those in remission are known to be at elevated risk of future MDEs. A common and distressing symptom of MDD is overgeneralised self-blame, and this also persists into remission. In order to study the involvement of self-blame in vulnerability to MDD, a large cohort of participants was recruited: a group with remitted MDD (rMDD) and a matched healthy control (HC) group with no personal or family history of MDD. Participants completed electrophysiological and neuropsychological tasks. The rMDD group also completed a 14-month follow-up period, during which symptoms were monitored at intervals; this was to study the predictive effects of electrophysiological and neuropsychological variables, with a view to developing a biomarker with predictive value. The main method was electroencephalography (EEG), chosen for its high temporal resolution in comparison to a commonly used technique, functional magnetic resonance imaging (fMRI). On a practical level, EEG is also more cost effective and widely available, making it more suitable for future clinical transfer of any biomarker developed. A task previously used in fMRI was adapted for EEG; in this task, short sentences designed to evoke negative feelings related to the self and others were presented. The theta signal was abnormally sustained over time during self-blame in the rMDD group relative to the HC group. Given the involvement of theta in temporal binding, this may represent a correlate of dysfunction within the neural network underpinning self-blaming emotions. Correlation of sustained theta with separately collected fMRI data indicated the dorsolateral prefrontal cortex (dlPFC) was involved in this network. In a source analysis of the EEG data, the dlPFC was identified again; it showed reduced activation in the rMDD group relative to the HC group during other-blame. In summary, activation of the dlPFC appears to be adaptive in both self- and other-blame, as the HC group showed higher activation than the rMDD group; further work is required to confirm the clinical relevance of this. For a separate study of memory overgeneralisation, a known feature of MDD, a novel associative memory task was designed. A loss of bias towards remembering positive memories was found in a subgroup of the rMDD cohort with early life stress (ELS). This reduced positive bias correlated with the number of past MDEs, indicating that the cumulative effect of MDEs reactivating early traumatic memories leads to selective loss of positive memory bias. In summary, although no electrophysiological or neurocognitive predictive markers of recurrence risk were found, clear effects were seen in the cross-sectional results. Importantly, EEG was also validated as a technique for detecting self-blame-selective neural correlates of depression vulnerability. There were clear effects in the temporal domain, which highlight the benefits of EEG above other imaging techniques. However, the sources identified did not correlate with parallel fMRI work, so further work is required to understand the temporal dynamics of these sources. This research provides a platform from which future EEG investigations can develop.
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Dedicated to Margaret Elizabeth Gethin.

General author acknowledgements

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Jennifer Gethin, Clifford Workman and Karen Lythe conducted telephone screening interviews. Karen Lythe and Jennifer Gethin completed initial clinical assessments and Roland Zahn confirmed all diagnoses. Karen Lythe, Roland Zahn and Clifford Workman conducted follow-up interviews.

Full details of chapter-specific author contributions precede each experimental chapter.
The author
Jennifer Gethin completed a BSc in Neuroscience at the University of Manchester in 2010. This included a year in industry as assistant manager of a clinical trials laboratory. She then continued on to do an MRes in Biological Sciences, which included a research project on cross-modal integration in autism spectrum disorders in the School of Psychological Sciences. She then remained in Psychological Sciences to pursue her PhD.

Alternative format
This thesis has been approved for submission in the alternative format. The experimental chapters were written in the style of scientific papers, with a view to submitting them to scientific journals for publication.

Other projects
In addition to the work presented in this thesis, the author has been involved in other projects leading to manuscripts at various stages in the publication process.


Workman, C., Lythe, K. E., McKie, S., Moll, J., Gethin, J. A., Deakin, J. F. W., Elliott, R., Zahn, R. Subgenual cingulate-amygdala functional disconnection and vulnerability to melancholic depression. (*Currently under review in Neuropsychopharmacology*)
Chapter 1: Introduction

1.1 Preface and aims
For many, major depressive disorder (MDD) is a recurrent condition (Solomon et al., 2000). Of course, this is disruptive to the lives of patients. The overarching aim of this thesis is to contribute to the understanding of depression vulnerability through the use of electroencephalography (EEG) and neuropsychological testing.

People with a previous major depressive episode (MDE) are known to be at increased risk of future episodes, a risk which increases further with each successive episode (Solomon et al., 2000). In order to study vulnerability to depression, a cohort of participants with remitted MDD (rMDD) was recruited, along with a matched healthy control (HC) group with no personal or family history of MDD. This allowed comparison of a high- and low-risk group to study vulnerability to future depression, without the confounding effects of differences in current mood state. rMDD participants also completed a 14-month follow-up period, during which symptoms were assessed at intervals to establish “Stable Remission” and “Recurring Episode” subgroups; this allowed predictive effects of study variables to be evaluated. Development of reliable biomarkers with predictive value of disease course are currently lacking (Savitz et al., 2013).

Various methods are used in this thesis, but at the core is the study of self-blame. MDD is often modelled as a disorder of increased negative affectivity and lowered positive affectivity (Watson et al., 1988), but blame attribution models emphasise an imbalance in these increased negative feelings (Abramson et al., 1978, Kinderman and Bentall, 1997). Those with MDD tend to exhibit blaming feelings towards themselves, leading to over-generalised feelings of guilt or worthlessness, listed as one of the MDD diagnostic symptoms (First et al., 2002). Indeed, 82% of our cohort reported feeling self-blaming emotions during depressive episodes, in contrast to 26% reporting anger or disgust towards others (Zahn et al., 2015b). This is termed the ‘self-blaming bias’.

The thesis will start with a review of the relevant MDD literature (Chapter 1), including previous electrophysiological and neuropsychological findings, with an emphasis on vulnerability. There will then be a General Methods chapter (Chapter
summarising the recruitment, tasks and major analyses used, along with a short discussion of each where appropriate. Four experimental chapters will then follow, which approach the topic in different ways. All chapters refer to the same cohort of participants, described above.

Chapter 3 investigates self-blame-related EEG signals using a task in which word stimuli describing negative social actions between the participant and their best friend are presented. The author adapted this task for use in EEG from a previous functional magnetic resonance imaging (fMRI) study (Green et al., 2012); EEG has higher temporal resolution than fMRI (Luck, 2014), so this allowed exploration of the signal over time. The EEG signal was also decomposed into different frequency bands to study self-blame-selective effects in the theta and alpha bands; these bands are known to show changes at rest in MDD (Olbrich and Arns, 2013). Predictive effects of both were also studied.

Chapter 4 further explores the same data as Chapter 3, using an EEG source approach; this follows on from previous fMRI research (Green et al., 2012). In those with rMDD compared to HCs, Green and colleagues found a self-blame-selective functional decoupling between the anterior temporal lobe (ATL; associated with knowledge of social concepts (Zahn et al. 2009; Zahn et al. 2007)) and the subgenual cingulate cortex (sgACC; associated with individual differences in guilt experience (Zahn et al. 2009)). This was interpreted as maladaptive integration of conceptual knowledge represented in the ATL when feeling guilt, resulting in the characteristic overgeneral feelings of self-blame (Green et al., 2012). More recently, a self-blame-selective hyperconnectivity between the same regions was shown to distinguish rMDD participants who subsequently developed a recurring episode from those who remained in stable remission (Lythe et al., in press); this confirms that abnormal functional connectivity of these areas is associated with vulnerability, although the direction of abnormality (hypoconnectivity or hyperconnectivity) requires clarification. In this chapter, EEG data were projected into the source space to explore analogous group differences, both in raw amplitude and in functional connectivity. Predictive effects were also studied.

Chapter 5 explores how well self-blame-related source signals from EEG correlated with equivalent source signals from fMRI (collected separately in the same
participants using the same task as part of the larger study this PhD project is affiliated with). Whilst the use of fMRI in researching self-blaming biases in MDD continues to be valuable (e.g. (Lythe et al., in press)), unfortunately the method has high associated costs (Luck, 2014) which make markers of prediction difficult to translate into clinical practice. EEG is much more cost effective (Luck, 2014), and also more widely available, making it a better candidate for clinical use. However, the spatial resolution of EEG is much poorer than fMRI (Luck, 2014), and EEG source localisation techniques have no unique solution (Pizzagalli, 2007). It was of interest to investigate cross-modality correlation on measures of self-blame, to indicate whether EEG alone could be sufficient in future clinical studies of the functional neuroanatomy of self-blame in MDD. Two regions of interest (containing the ATL and sgACC) were explored.

*Chapter 6* takes a non-imaging approach, using a novel associative memory for social actions task developed by the author. This was based on previous research (Green et al., 2012) showing self-blame-selective decoupling between the hippocampus and the ATL, in rMDD relative to HC groups. This functional decoupling was hypothesised to represent a self-blame-selective deficit in accessing associative memories for specific temporal and spatial contexts of social actions. The aim was to use the specifically designed task to identify the hypothesised deficit in an rMDD population compared to an HC group, and also identify any predictive effects.

### 1.2 Major depressive disorder: symptoms and vulnerability

MDD is a form of unipolar depression. It is a lifetime diagnosis, characterised by one or more MDEs. In an MDE, at least five out of nine core symptoms are present, causing distress or impairment most of the time for at least two weeks: low mood, loss of interest/pleasure, appetite changes, sleep disturbances, psychomotor/energy changes, feelings of worthlessness/excessive guilt, reduced concentration and suicidal thoughts (First et al., 2002).

Whilst criteria such as this are useful in clinics and research, it is acknowledged that depressive symptoms exist on a continuum of intensity and chronicity with the natural human experience; there is growing support for proposals of a continuous rather than discrete classification system (Klein, 2008). Indeed, some large
taxometric studies have indicated that MDD is best characterised by a dimensional system (Hankin et al., 2005, Prisciandaro and Roberts, 2005), yet others have favoured discrete classification (Solomon et al., 2006). Although taxonomic studies indicate that discrete classification systems such as the Diagnostic and Statistical Manual for Mental Disorders (DSM) may not be optimal, it is the current gold standard for research purposes; the use of an international system across studies allows consistency and therefore more reliable comparisons.

A past MDE confers vulnerability to a future recurrence, a risk which increases with each subsequent episode (Solomon et al., 2000). Approximately 50% of patients will have a recurrence after their first MDE (Eaton et al., 2008), which demonstrates a need to identify those most at risk; this could inform prophylactic treatment (Savitz et al., 2013). The number of previous MDEs and time elapsed since the last MDE have been associated with recurrence risk (Solomon et al., 2000), but more robust markers would be clinically useful.

Studying a group of individuals with rMDD and a group of never-depressed HCs, without elevated risk of MDD through first-degree family history (Weissman et al., 2000, Wilde et al., 2014), allows comparison of groups at high and low risk for recurrence respectively. In the absence of residual symptoms, differences on study variables may represent vulnerability factors; differences between “Stable Remission” and “Recurring Episode” subgroups would further validate this. This is the rationale of the overall PhD study design.

1.3 Models of MDD

The mechanism underlying MDD remains unclear. It is apparent that multiple interacting factors are involved. Many cognitive and neurocognitive models based on clinical observations and experimental research have been postulated; key models and evidence to support them are discussed below.

1.3.1 Cognitive models of MDD

An early influential model was put forward by Beck and his colleagues. They proposed a triad of cognitive impairments in which the individual has a negative view of themselves and a negative perception of their experiences, leading to negative expectations of the future (Beck et al., 1979). This triad is kept stable, despite any contradictory evidence, by depressive styles of thinking (termed
‘schemas’), which influence attention to and interpretation of aspects of situations, further perpetuating the schema (Beck et al., 1979). Schemas are thought to be developed in early life (Bebbington, 1985) and can remain dormant until activated by a relevant stimulus, such as a stressor (Beck et al., 1979, Bebbington, 1985). In chronic depression, these depressive schemas become the dominant cognitive style, regardless of external circumstances (Beck et al., 1979). This fits with the evidence that higher numbers of past MDEs increases risk for an individual developing another MDE (Solomon et al., 2000); with increasing depression history, the schema may become more dominant and easily activated.

Another prominent model, the learned helplessness model, was revised in 1978 (Abramson et al., 1978) in response to criticism that the original model, developed in animals, did not translate well to humans (Bebbington, 1985). The theory is built around situations where an individual fails to dictate a desired outcome, and subsequently tries to understand why. Where the attribution of failure is placed is key; vulnerability to MDD is associated with attributions which are internal (the cause is self-specific, i.e. not blaming others, and others would not fail in the same circumstances), stable (due to a factor which persists over time, e.g. lack of ability) and global (generalises to other situations). The authors propose that overgeneralisation of these attributions to future similar and dissimilar tasks results in lack of motivation and depressed affect (Abramson et al., 1978). An individual’s ‘attributional style’ is perhaps comparable to Beck’s schemas. It has been shown that depressed individuals are more likely to attribute their failure at a task to their own inadequacy, in contrast to HCs who blamed the task complexity (Rizley, 1978). In comparison to HCs, depressed patients have also been shown to attribute hypothetical negative social situations to internal factors, indicating higher levels of self-blame (Kinderman and Bentall, 1997). The level of internality of attributions in negative situations can also be influenced by recent events in those who are already depressed (Bentall and Kaney, 2005). This can be explained by the attribution-self-representation cycle (Bentall et al., 2001); negative internal attributions after events inform self-representations in a negative way, which in turn influences mood. The updated self-representations ultimately inform future attributions, forming the eponymous cycle.
A further update of the learned helplessness model (Abramson et al., 1989) reduced the emphasis on the role of internality, stating that in some situations, internality may be adaptive; for example, failure attributed internally may result in increased effort and success in future similar situations. The focus is placed on global and stable qualities of attributions (Abramson et al., 1989). Indeed, the Temple-Wisconsin vulnerability study showed that non-depressed participants who were classed as “cognitively high-risk” based on factors including global and stable attributions, showed higher and more severe incidences of MDD later in life (Alloy, et al. 2000).

It has also been noted that attributional style is not as stable as previously thought. It varies dependent on mood state; a mild depressive state in those vulnerable to depression activates negative attributional styles that further perpetuate depressed mood (Teasdale, 1988). Pessimistic attributions have indeed been seen more with low mood compared to euthymia (Miranda and Persons, 1988).

### 1.3.2 Self-blame in MDD

MDD is often modelled as a disorder of increased general negative affectivity and lowered positive affectivity (Watson et al., 1988). However, a common theme across the models discussed above is that of increased negative emotions, but only directed towards the self: the ‘self-blaming bias’. Beck’s model specifies that the negative view of the self involves feelings of inadequacy and worthlessness, whereas others are not devalued in this way (Beck et al., 1979). The revised learned helplessness model discusses internal, self-specific attributions (Abramson et al., 1978) and the attribution-self-representation cycle suggests that these are informed by negative self-representations (Bentall et al., 2001). The importance of self-blame is also noted in the diagnostic criteria for an MDE, which include the self-blaming feelings of guilt and worthlessness, but not negative emotions directed at others (‘other-blaming’ emotions) (First et al., 2002).

Interestingly, in a meta-analysis of largely non-clinical studies, the level of maladaptive guilt and shame was associated with depressive symptoms (Kim et al., 2011), potentially representing a vulnerability factor for future depression onset. Excessive self-blame has been shown to predict increased likelihood of a subsequent MDE in both pre-school children (Luby and Belden, 2012) and adolescents (Kouros et al., 2015).
Guilt in its adaptive form is a pro-social emotion (O'Connor et al., 2011). It is natural to blame oneself for inappropriate actions or failures; the subsequent feelings of guilt could be considered to be an evolutionary advantage in humans, as we are social animals and guilt encourages corrective behaviour (Tangney et al., 1992, Amodio et al., 2007). However, the pathological guilt observed in MDD is different, being defined as “excessive and inappropriate” in the diagnostic criteria (First et al., 2002). Berrios and colleagues describe two forms of pathological guilt in MDD: ‘delusional guilt’, experienced after imaginary misdeeds, or in excess when the misdeed is minor, and ‘affective guilt’, experienced despite the individual being unable to give a reason why (Berrios et al., 1992). O’Connor and colleagues have proposed further subtypes of interpersonal guilt which associate with MDD: survivor guilt and omnipotent responsibility guilt (O'Connor et al., 1997, O'Connor et al., 2002).

Survivor guilt, originally associated with World War II survivors (Blacher, 2000), is the guilt experienced for being more fortunate than others; the notion that personal success will somehow disadvantage others or cause them to feel inferior (Blacher, 2000, O'Connor et al., 2002). It is thought to have evolved to encourage sharing in social groups to promote survival (O'Connor et al., 2002), but becomes damaging to the individual when efforts to prevent guilt result in self-destructive or submissive behaviour (O'Connor et al., 2002, O'Connor et al., 2007). Omnipotent responsibility guilt stems from excessive and persistent feelings of concern for the welfare of others (O'Connor et al., 2002), possibly similar to Berrios’s affective guilt. Omnipotent responsibility guilt could lead to ‘hyper-altruistic’ behaviour, which is associated with MDD (O'Connor et al., 2007, O'Connor et al., 2011). Interestingly, elevated survivor guilt and omnipotent responsibility guilt have also been shown in rMDD (Green et al., 2013b).

Shame, another self-blaming emotion, has also been associated with MDD (Ghatavi et al., 2002), albeit with reduced frequency when compared to guilt (Zahn et al., 2015b). Although they are similar emotions, guilt and shame are not synonymous (Tangney et al., 2007). An individual is likely to feel guilt after negative behaviour as a result of concern for its impact on others, but shame for how others may judge them (Tangney et al., 2007); guilt is linked to actions (“behavioural self-blame”) and shame to judgement of the whole self (“characterological self-blame”) (Janoff-Bulman, 1979). Guilt and shame are therefore thought to moderate behaviour in
different ways: guilt is prescriptive, acting to motivate positive behaviours, whereas shame is proscriptive, resulting in avoidance of negative behaviour (Sheikh and Janoff-Bulman, 2009). Just as guilt can be overgeneralised, as discussed above, shame can be overgeneralised to become worthlessness (Tangney et al., 2007), a symptom that is listed in the diagnostic criteria for an MDE (First et al., 2002). It is still debated in the literature as to which emotion is more prominently associated with depression: guilt (Alexander et al., 1999, Zahn et al., 2015b) or shame (Highfield et al., 2010, Orth et al., 2006, Thompson and Berenbaum, 2006). Variation in findings is possibly due to the range of measures used in the different studies, and also differences in defining the concepts of guilt and shame to participants, a difficulty that is acknowledged in the literature (Kim et al., 2011, Tangney et al., 2007). It is likely that both guilt and shame have a role to play in MDD (Kim et al., 2011). Like guilt (Green et al., 2013b), increased shame-proneness has also been seen in rMDD (Thompson and Berenbaum, 2006).

Additionally, other forms of overgeneral self-blame should be considered. Self-hate, a characterological form of self-blame related to shame (O'Connor et al., 1997), has been shown to be elevated in rMDD (Green et al., 2013b). Self-contempt bias, which specifically explores overgeneralised self-blaming feelings towards oneself relative to others, correlates with self-hate and is also elevated in rMDD (Green et al., 2013b).

Maladaptive changes in the quality of self-blame-related emotions may be a result of decreased differentiation of social concepts when judging one’s own negative behaviour relative to that of others (Green et al., 2013a). Conceptual differentiation is thought to be needed to enrich feelings with specific meaning so that the feeling can be better related to the behaviour (i.e. “When I dropped my friend’s laptop, my behaviour was clumsy” rather than “my behaviour was bad”) (Moll et al., 2005). Consistent failure to differentiate between the range of negative self-related concepts could over time lead to the overgeneral forms of self-blame discussed above (Green, 2011).

1.3.3 Moral cognitive neuroscience models of MDD
Given the prominent role of self-blame in MDD, models of moral cognition are relevant. Moral motivations are driven by social knowledge about a particular set of
cultural, social and personal values and the needs of others within that culture (Zahn et al., 2011). Behaviours which conform to or transgress social values evoke moral emotions dependent on the valence and agent of the action (Moll et al., 2008). Moral emotions include the self-blaming emotions of guilt and shame, but also other-blaming emotions (e.g. indignation), self-praising emotions (e.g. pride) and other-praising emotions (e.g. gratitude) (Zahn et al., 2013). They encourage evaluation, correction (Tangney et al., 1992) and future alteration (Tangney et al., 2007) of our behaviour so that we conform to the socio-cultural norm. This is important as humans are social animals (Moll et al., 2005).

However, moral emotions can become dysfunctional in MDD, as previously discussed. Models of moral cognitive neuroscience can help us elucidate the mechanisms behind the self-blaming bias. Key models will be discussed below in the context of behavioural, neuroimaging and lesion data.

1.3.3.1 Dual process model
Greene and colleagues put forward a cognitive control model for moral judgement, known as the dual process model (Greene et al., 2004, Greene, 2007). They propose that during moral decision making, there is competition between areas representing reason and emotion, and the more dominant area determines the resultant judgement or behaviour (Greene et al., 2001).

The dual process model was originally developed using a forced choice moral dilemma task with an HC group undergoing fMRI. The task included three conditions in which scenarios were accepted or rejected by the participant: ‘personal’ moral dilemmas, involving directly causing harm and therefore thought to be more emotionally difficult decisions (e.g. “throwing people off a sinking lifeboat”); ‘impersonal’ moral dilemmas, with the potential to cause equivalent harm, but without direct involvement (e.g. “voting for a policy expected to cause more deaths than its alternatives”); ‘non-moral dilemmas’ (e.g. “whether to travel by bus or train”). The medial frontal, posterior cingulate and angular gyri, which the authors associated with emotional processing, were more activated in the personal moral condition compared to both other conditions. There was also decreased activation in the dorsolateral prefrontal cortex (dPFC), which the authors associated with working memory. Despite the similarity in outcome between personal and
impersonal dilemmas, people tended to endorse impersonal actions much more than personal ones; Greene and colleagues propose that increased emotional processing during personal dilemmas out-competes the rational response (Greene et al., 2001).

Further work extended personal vs. impersonal activation responses to a larger ventromedial prefrontal cortex (vmPFC) and subcortical limbic network. This work also showed that, during high-conflict (i.e. more difficult) personal moral dilemmas, dIPFC activity increased when utilitarian vs. non-utilitarian decisions were made; this was interpreted as increased reasoning and cognitive control during judgements overpowering the natural emotional response, resulting in a utilitarian outcome (Greene et al., 2004). Further evidence stems from supposed ‘emotional blunting’ after bilateral lesions including the vmPFC (Greene, 2007); such patients displayed increased utilitarian responses to high-conflict moral dilemmas relative to controls with brain damage outside the vmPFC and an HC group (Koenigs et al., 2007). Within the dual process model, this result is explained by reduced competition of the emotional response allowing cognitive control and utilitarian responses to prevail (Greene, 2007).

However, it would appear that this emotional blunting is not absolute; in the Ultimatum Game\(^1\), such lesion patients are less likely to accept unfavourable monetary offers when compared to an HC group (Koenigs and Tranel, 2007). This suggests that the vmPFC lesion patients had not only an intact but an enhanced anger response (Pillutla and Murnighan, 1996). Conversely, reductions in prosocial emotions have been seen in ventral frontal lesion patients (Anderson et al., 1999, Damasio et al., 1990). If they can experience anger, but not prosocial emotions, this suggests a separation of prosocial and other-blaming emotions within the frontal cortex (Moll and de Oliveira-Souza, 2007). This has implications for the specificity of emotional processing within the dual process model. Additionally, there is concern that some lesions in the Koenigs papers spread into dorsolateral areas; in this case, the dual processes of reason and emotion should be equally affected (Moll and de Oliveira-Souza, 2007). Greene’s research could also be criticised for use of

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\(^1\)The Ultimatum Game is a two-player game. The ‘proposer’ is repeatedly given an amount of money to split as they desire. If the ‘responder’ deems it fair, they accept and the money is split as proposed. If they deem it unfair, they reject it and neither player receives any money. The idea is that the proposer will offer as little money as they think the responder will accept. Low offers are normally accepted by the responder, given that some money is better than none; very low offers may be rejected, despite being counterproductive, in order to punish the proposer (Sanfey et al., 2003).
unrealistic extreme moral dilemmas. For example, a high-conflict personal moral dilemma such as “throwing people off a sinking lifeboat” (Greene et al., 2001) does not represent a situation true to everyday real life; participants may struggle to predict their real-world responses to such novel scenarios, and engage different mechanisms as a result (Casebeer, 2003, Knutson et al., 2010).

1.3.3.2 Somatic marker hypothesis

Damasio and colleagues suggest the somatic marker model of moral decision-making, which includes a different role for the vmPFC (Damasio et al., 1990). This model is based on the concept that socially appropriate decision-making and behaviour depends upon the ability to predict the outcome of actions and how that may impact upon others. They hypothesise that non-conscious ‘somatic markers’ (different autonomic states representing emotional reactions to the outcomes of different possible decisions) are generated by the ventral PFC in response to social stimuli (Damasio et al., 1990).

Impairments in social decision-making have been observed in patients with lesions in the vmPFC, most notably patient EVR (Eslinger and Damasio, 1985). His life was severely impaired by his ‘acquired sociopathy’, yet strangely he was not impaired in experimental social decision-making tasks with short-term consequences (Saver and Damasio, 1991). This does not suggest a general impairment in social knowledge, which does not match his everyday behaviour. One possible explanation is that, contrary to real-life decisions, the tasks did not involve making decisions from his own perspective, but as an observer. Additionally, the timeframe of the tasks was artificially compacted relative to the speed with which real-life decisions are made (Saver and Damasio, 1991); potentially this made it easier for EVR to see the ‘big picture’.

Damasio’s group offers further evidence for the somatic marker hypothesis from patients with lesions similar to EVR playing the Iowa Gambling Task. This task addresses the concerns of both perspective and timeframe. In this task, healthy participants learned over time which decks provided the most favourable outcome

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2In the Iowa Gambling Task, the participant is presented with four apparently identical card decks. The cards contain a series of monetary gains and/or losses. The player is told to maximise their winnings by selecting cards from whichever combinations of decks they wish until told to stop by the experimenter. Unbeknownst to them, the card decks are fixed so that some give bigger gains but even larger losses (and vice versa) over the course of the game (Bechara et al., 1994)
and subsequently only selected cards from those decks. In contrast, lesion patients continued taking cards from the high-risk decks, ultimately leading to larger losses over the course of the game. EVR showed no improvement when tested at intervals over the subsequent six months, suggesting a persistent impairment, which reflects his real-life behaviour. The authors conclude that EVR-like patients are driven by immediate prospects at the expense of future consequences (Bechara et al., 1994). Contrary to the HC group, patients with vmPFC lesions also do not develop anticipatory skin conductance responses whilst selecting risky cards. The authors suggest that these non-conscious somatic markers guide behaviour, and their absence in the lesion group results in poorer decision-making (Bechara et al., 1996, Bechara et al., 1997). Bechara and colleagues also claim that HC participants develop such physiological responses before being consciously aware of which decks are advantageous; conversely lesion patients do not develop physiological responses even after becoming consciously aware of the high- and low-risk decks (Bechara et al., 1997). However, Maia and McClelland have subsequently shown that HC participants are aware of their strategy as soon as they begin making sensible decisions; they suggest an alternative hypothesis that somatic markers may not be necessary for decision-making and may simply reflect an emotional response to consciously considering a risky decision, which is absent in the lesion patients (Maia and McClelland, 2004).

1.3.3.3 Event-feature-emotion complex model

Moll and colleagues present a fronto-temporo-mesolimbic model of moral cognition: the event-feature-emotion complex (EFEC) model (Moll et al., 2005). They propose that integration of a triad of elements is necessary for the correct understanding and practice of social and moral behaviour: 1) context-independent representations of social concepts, 2) sequential event knowledge in the context of social actions and 3) basic emotional and motivational states.

The first component, social conceptual knowledge, is defined as non-episodic knowledge representing the fundamental meaning of abstract concepts; the term describes social behaviour as a specific form of semantic memory (Tulving, 1986). For example, just as the core concept of a car can be understood across different brands from Mini to Range Rover, the core of social concepts like “stinginess” can be understood across different social action contexts, i.e. not donating money to a
friend’s charity collection, leaving the pub before it’s your round or not offering your elderly neighbour a lift home in the rain. Social conceptual knowledge allows us to understand and judge our own behaviour and that of others (Moll et al., 2005). Conceptual representations are formed over time by statistical learning mechanisms that take into account the different modalities of a given concept and extract the core meaning (Rogers et al., 2004). Clinical evidence has associated conceptual knowledge with the ATL; pan-modal (i.e. auditory, visual, olfactory) conceptual deficits are seen in semantic dementia patients, who display marked ATL atrophy (Lambon Ralph and Patterson, 2008). This deficit is selective to conceptual knowledge (Hodges et al., 1992) and semantic task impairment correlates with the level of ATL atrophy (Mummery et al., 2000). These semantic deficits are not limited to concrete concepts, but include more abstract concepts including human actions (Lu et al., 2002). Studies in HC participants have also indicated involvement of the ATL in conceptual knowledge tasks: for example, the ATL was activated bilaterally in an fMRI task of object categorisation (Visser et al., 2010), and repetitive transcranial magnetic stimulation of the temporal poles resulted in impairment on a synonym judgment task (Pobric et al., 2009). Theory of mind tasks, which require understanding of the social actions of others, also lead to ATL activation (Frith and Frith, 2003, Olson et al., 2007). The right ATL in particular has been associated with social concepts. Disruption in social behaviour has been seen with volumetric loss (Rankin et al., 2006) and hypoperfusion (Mendez et al., 2000) in the right ATL. The right superior ATL was consistently activated during the experience of moral feelings (e.g. guilt, indignation, pride) regardless of the valence or the agency; the level of activation also correlated with increasing conceptual detail of the stimuli (Zahn et al., 2009c). Frontotemporal lobar degeneration patients have also shown hypometabolism in the right superior ATL, which correlated with impairment on a social concept task and with their general level of socially inappropriate behaviour (Zahn et al., 2009b). However, a recent meta-analysis found no evidence of lateralisation of social concepts, but did confirm their association with the ATL bilaterally (Rice et al., 2015).

The second component of the EFEC model is sequential event knowledge, which is critical for the successful prediction of the consequences of the actions of oneself and others; this enables understanding of how to act to produce the best outcome
Sequential event knowledge is stored in the form of context-dependent sequences and is linked to the PFC (Grafman, 1995). Patients with PFC lesions fail to correctly order events in a sequence (Sirigu et al., 1995, Sirigu et al., 1996). Subdivisions of the PFC are thought to have specific roles (Moll et al., 2005). The vmPFC is thought to be important for social and emotional sequences (Wood and Grafman, 2003). This could explain why patients with vmPFC lesions, such as EVR, make poor social decisions (Eslinger and Damasio, 1985) as they cannot foresee the consequences. More routine, everyday sequences are linked to medial and posterior areas of the PFC (Moll et al., 2005, Wood, 2004), whereas complex long-term consequences involving future planning are stored anteriorly (Moll et al., 2005, Wood and Grafman, 2003).

The final component of the EFEC model entails basic, undirected emotional and motivational states. These include anxiety and attachment, which are necessary for moral motivation; without the motivation to act, understanding of a given situation is purposeless. Motivational states are represented by limbic and paralimbic regions (Moll et al., 2005). Increased aggression has been seen after hypothalamic tumours (Weissenberger et al., 2001) and even transiently during neurostimulation of this area (Bejjani et al., 2002). Volumetric reductions in the sgACC also correlated with reduced empathy in patients with anti-social personality disorder (de Oliveira-Souza et al., 2008). In HC groups, the hypothalamus has been associated with attachment (Swain, 2008) and the septal and sgACC region with compassion (Kim et al., 2009).

In contrast to the ATL (which is consistently activated during the experience of moral feelings, regardless of the valence or the agency (Zahn et al., 2009c)), the pattern of limbic activation is feeling-specific i.e. context-dependent. For example, the contrasting emotions of guilt and anger have selectively been associated with activations in the sgACC and lateral orbitofrontal cortex respectively (Zahn et al., 2009c).

The integration of the three components of the EFEC model allows the moral understanding of a given situation, prediction of possible consequences of actions and produces the motivational feeling to act to produce the optimal outcome. The combination leads to moral feelings such as guilt, pride and gratitude (Moll et al., 2005). An example of this is linked to the prevention of stingy behaviour like “not offering your elderly neighbour a lift home in the rain”: 1) the ATL allows
understanding of the concept of the neighbour’s helplessness against the rain, 2) the PFC allows representation of the consequences of not acting (i.e. the neighbour will get soaked on their walk home, and may become ill as a result) and 3) limbic regions activate social attachment to the neighbour. In combination, this leads to the moral feeling of compassion, which drives the desire to help (NB. this example was modified from one in (Moll et al., 2005)). Dysfunction in any one region of the model can therefore result in deficits in social cognition and decision-making. This provides a framework with which to explore the neural correlates of moral emotions in MDD.

The author favours the EFEC model, as it provides explanations for inconsistencies in the other models. Firstly, the dual process model states that vmPFC lesions should result in general emotional blunting (Greene, 2007). The EFEC model suggests vmPFC lesions would cause a selective reduction in prosocial feelings (Moll et al., 2005), which explains why they behave in a more utilitarian fashion during moral dilemmas (Koenigs et al., 2007), yet display increased anger during the Ultimatum Game (Koenigs and Tranel, 2007). Secondly, the EFEC model could also explain why patient EVR was not impaired in experimental social decision-making tasks with short-term consequences (Saver and Damasio, 1991). According to the EFEC model, despite the vmPFC being important for social and emotional sequences (Moll et al., 2005), EVR’s performance could have been facilitated by preserved posterior parts of the vmPFC (Eslinger and Damasio, 1985); posterior parts are thought to store knowledge of routine sequences (Moll et al., 2005), such as those given to EVR (Saver and Damasio, 1991). Tests of long-term consequences true to real-life were not administered (Saver and Damasio, 1991), and may have been more successful in identifying an experimental correlate of EVR’s decision-making deficit. Given the strong evidence in favour of the EFEC model, neuroimaging findings in the next section will only be discussed in the context of this model.

1.4 Neuroimaging findings in MDD

Advances in the diverse field of neuroimaging over the past few decades have permitted a surge of research into the neurobiological mechanisms behind MDD.
1.4.1 Structural findings

Human lesion studies allow links between brain areas and cognitive functions to be explored. A large study was conducted on patients with acquired head injury and stroke with lesions in various areas of the PFC. Those with lesions in the vmPFC scored significantly lower on a depression rating scale than controls with no PFC lesion; in contrast, those with dIPFC lesions scored significantly higher (Koenigs et al., 2008). The vmPFC result fits with the interpretation that lesions in such areas would lead to a reduction in pro-social emotions (de Oliveira-Souza et al., 2008, Kim et al., 2009), which are often elevated in MDD (First et al., 2002). Interestingly, one study participant acquired their vmPFC lesion attempting suicide, which both subjectively and objectively alleviated their depressive symptoms (Koenigs et al., 2008).

MDD is not associated with a general decrease in brain volume, but reductions specific to frontal regions are evident (Arnone et al., 2012, Koolschijn et al., 2009). Volumetric meta-analyses consistently identify atrophy in the hippocampus in current MDD (Arnone et al., 2012, Campbell et al., 2004, Koolschijn et al., 2009, Videbech and Ravnkilde, 2004), and this also correlates with duration of depression (Bell-McGinty et al., 2002, MacQueen et al., 2003, Videbech and Ravnkilde, 2004). This is possibly due to neurotoxic effects of the increased cortisol levels (Sapolsky et al., 1985) which have been observed in MDD (Gold and Chrousos, 2002); the hippocampus has a high level of glucocorticoid receptors, making it particularly susceptible to increased cortisol levels (Lorenzetti et al., 2009). Indeed, it has been suggested that effective antidepressant medications reverse atrophy by promoting hippocampal neurogenesis (Sahay and Hen, 2007), as duration of medicated MDEs did not correlate with hippocampal shrinkage like unmedicated episodes did (Sheline et al., 2003). Additionally, hippocampal reductions were not seen in rMDD groups compared to HC groups (Arnone et al., 2013, Kempton et al., 2011). In a longitudinal study, those with current MDD showed hippocampal reductions in keeping with the literature, but this normalised after citalopram treatment, indicating hippocampal volume is a state not a trait marker of MDD (Arnone et al., 2013). The hippocampus is not directly named in the original EFEC model (Moll et al., 2005), but has been implicated since (see Section 1.4.2). The hippocampal involvement in
memory encoding and retrieval (Gilboa et al., 2004) also links to memory deficits seen in MDD (see Section 1.5.1).

Atrophy in other frontal areas has been noted in MDD, but none as consistently as the hippocampus (Arnone et al., 2012), so these will not be considered further.

1.4.2 fMRI/PET

Functional imaging techniques such as positron emission tomography (PET) and fMRI are valuable for observing abnormalities in brain activity, rather than just static structure. It is beyond the scope of this thesis to provide a thorough review of the vast functional neuroimaging literature in MDD, so key findings related to self-blame and MDD will be discussed.

In HC groups, activity in the sgACC has been associated with the experience of guilt and empathic concern (Zahn et al., 2009c, Zahn et al., 2009a). Interestingly, the sgACC displays consistent abnormalities in MDD. This area shows altered perfusion and metabolism in MDD (Drevets et al., 1998, Ebert and Ebmeier, 1996), abnormalities which respond to antidepressant treatment (Ressler and Mayberg, 2007). The sgACC is also a target for deep brain stimulation in treatment-refractory MDD (Mayberg et al., 2005). In studies of self-referential processing of negative stimuli in symptomatic MDD, the sgACC has not been identified (Grimm et al., 2009, Lemogne et al., 2009, Lemogne et al., 2010). However, the sgACC was shown to be activated during a charitable donation task in an rMDD group. Due to the previously demonstrated connection between the sgACC and guilt, the authors suggested a link to residual guilt driving altruistic decisions (Pulcu et al., 2014b).

Standard neuroimaging analyses, such as the fMRI blood-oxygenation-level dependent analysis, explore brain regions as independent units. Whilst this is informative, models such as the EFEC model indicate that functional integration is key (Moll et al., 2005), therefore connectivity analyses such as PPI analyses (Friston et al., 1997) have become increasingly important (see Section 2.3.5 for more information on PPI). The sgACC is consistently identified in aberrant functional networks during resting-state studies in adults with symptomatic MDD (Greicius et al., 2007, Seminowicz et al., 2004, Sheline et al., 2010) and similar results have also been seen in rMDD in young children (Gaffrey et al., 2012).
Recently, Green and colleagues (Green et al., 2012) conducted an fMRI study in rMDD and HC groups using a social action judgement task designed to evoke moral emotions associated with blaming the self and others (the value-related moral sentiment task, VMST; see Section 2.2 for a thorough description). Using a PPI analysis, the authors identified four regions which showed guilt-selective functional disconnection from the right superior ATL seed region in the rMDD group relative to the HC group: 1) the sgACC and adjacent septal region (SCSR), 2) the medial frontopolar cortex, 3) the right hippocampus and 4) the lateral hypothalamus (see Figure 1.1). The ATL was chosen as a seed region due to its role in representations of social conceptual knowledge (see Section 1.3.3.3), a key part of the EFEC model (Moll et al., 2005). The first component, the SCSR, is associated with the experience of guilt in HC groups (Zahn et al., 2009c, Zahn et al., 2009a). The authors state that although the precise function of the SCSR within this network is unclear, it is important in guilt, and the ATL may act to enrich this feeling with differentiated meaning. This allows interpretation of behaviour at the appropriate level of detail (i.e. “stingy”, “clumsy” or “boastful” rather than “bad”). The level of ATL-SCSR decoupling also correlated with elevated self-hate, further validating its involvement in maladaptive self-blame (Green et al., 2012). Secondly, the medial frontopolar cortex is associated with contextual information about the consequences of social actions (Moll et al., 2005). Decoupling of this area from the ATL could affect how the consequences of one’s actions are perceived, possibly driving the delusional or excessive guilt seen in MDD after minor transgressions (Berrios et al., 1992, First et al., 2002). Thirdly, the hippocampus is important in autobiographical memory formation and retrieval (Gilboa et al., 2004). Overgeneralisation of autobiographical memories (i.e. loss of detail) is a known characteristic of both symptomatic (Liu et al., 2013) and rMDD (Spinhoven et al., 2006), and is discussed further in Section 1.5.1. Failure to integrate specific details of autobiographical memories whilst evaluating one’s own behaviour may fuel negative overgeneralisations of the self by stripping memories of specific meaning (Green et al., 2012), i.e. “my past behaviour was careless” rather than “bad”). Due to loss of detail, dissimilar self-negative memories may be grouped together. Lastly, the hypothalamus is associated with attachment (Swain, 2008). Reduced integration of social action concepts with the state of attachment could lead to the “free-floating” omnipotent responsibility guilt associated with symptomatic (O’Connor et al., 2002) and rMDD (Green et al., ...)
2013b). It is important to re-iterate that these functional disconnections were self-blame-selective; intact physiological coupling, and therefore structural connections, were present in the rMDD group (Green et al., 2012).

![Figure 1.1 Guilt-selective functional decoupling in rMDD](image)

**Figure 1.1 Guilt-selective functional decoupling in rMDD** When compared to the HC group (yellow), the rMDD group (blue) showed functional disconnection within a fronto-temporo-mesolimbic network. Abbreviations: ATL, anterior temporal lobe; FPC, frontopolar cortex; HIPP, hippocampus; HYPO, hypothalamus; L, left; MDD, major depressive disorder; R, right; SCSR, subgenual cingulate cortex and adjacent septal region. Image taken from (Green et al., 2012).

### 1.4.3 EEG

EEG is another non-invasive functional imaging technique. EEG uses scalp electrodes to detect summed post-synaptic potentials (Pizzagalli, 2007, Fabiani et al., 2007). The simplest analysis is at scalp level: the signal is averaged during a given condition, and deflections in the resultant waveform time-locked to stimulus onset are analysed in terms of amplitude and latency. Deflections are traditionally named after their direction and latency, e.g. P300 is a positive deflection originally found to peak around 300 ms after stimulus presentation (Luck, 2014). Data can also be projected into the brain space using source localisation techniques (Litvak et al., 2011), enabling analysis techniques analogous to those used with fMRI. EEG data can also be broken down into its component frequency bands (Litvak et al., 2011);
the most consistent findings in MDD have been observed at rest in the theta and alpha frequency bands (Olbrich and Arns, 2013).

Elevated resting theta power has been found to distinguish MDD patients from an HC group in a large study (Grin-Yatsenko et al., 2010). Possible generators of increased theta have been localised to the frontal cortex (Arns et al., 2015, Korb et al., 2008), rostral anterior cingulate cortex (Arns et al., 2015, Korb et al., 2008) and the sgACC (Jaworska et al., 2012). These regions all link to the EFEC model (Moll et al., 2005). Given the supposed role of theta in synchronisation of distributed brain areas (O’Neill et al., 2013, Klimesch, 1999, Jones and Wilson, 2005), it could be argued that these theta findings reflect problems with the temporal binding of components of the EFEC model during ongoing self-blaming processes.

Elevated resting alpha power has also been found in MDD across multiple scalp sites: frontal (Jaworska et al., 2012), parietal (Jaworska et al., 2012, Grin-Yatsenko et al., 2010) and occipital (Grin-Yatsenko et al., 2010). In contrast, one study found decreased alpha in frontal, parietal and occipital areas; this persisted into remission after fluoxetine treatment (Almeida Montes et al., 2015). Frontal alpha asymmetry has also been extensively investigated after early influential work found increased left prefrontal alpha activity in symptomatic MDD (Henriques and Davidson, 1991) and also rMDD (Henriques and Davidson, 1990) compared to an HC group; increased alpha was interpreted as hypoactivation leading to “deficits in the approach system”, which is associated with anhedonia (Henriques and Davidson, 1991). However, many studies have since failed to replicate their findings (Carvalho et al., 2011, Gold et al., 2013, Reid et al., 1998, Segrave et al., 2011); of particular note, one study in elderly participants found no difference in frontal alpha asymmetry between HC, rMDD and symptomatic MDD groups (Carvalho et al., 2011). The prominent Henriques and Davidson study has since been criticised for group differences being driven by a few individual participants (Olbrich and Arns, 2013). The involvement of alpha asymmetry in MDD therefore remains unclear.

Other than those previously mentioned, there are few studies using EEG in rMDD. One such study collected resting-state EEG data in rMDD, symptomatic MDD and HC groups. The rMDD group displayed reduced theta in frontal regions compared to both other groups, and reduced alpha in frontal regions compared to the HC group.
Given elevated theta and alpha in frontal regions are seen in symptomatic MDD, this result could represent a compensation mechanism. Another study used an emotional Stroop task\(^3\) in rMDD, symptomatic MDD and HC groups whilst EEG was recorded. Currently depressed participants showed increased interference (longer response times) to negative compared to positive emotional stimuli, which was not seen in the other two groups. However, both rMDD and current MDD groups showed an enhanced N450 to negative stimuli at parietal sites. The authors suggest that this reflects a trait increased attention to negative stimuli, although this is at odds with the rMDD response time data (Dai and Feng, 2011). An emotional oddball task revealed an enhanced P300 to rare negative words relative to frequent neutral words in a symptomatic MDD group relative to rMDD and HC groups. This was interpreted as heightened attention to negative emotionality in the depressive state which does not persist into remission (Ilardi et al., 2007).

EEG studies of self-blaming emotions in rMDD are currently lacking; these may be more likely to detect effects than studies using non-specific negative stimuli. Studies within this thesis have been designed to fill that gap (see Chapters 3 and 4).

### 1.4.4 Biomarker development

An important clinical application of neuroimaging research in MDD is biomarker development. A biomarker is defined “a characteristic that is objectively measured and evaluated as an indicator of normal biologic[al] processes, pathogenic processes, or…responses to a therapeutic intervention” (De Gruttola et al., 2001). Generally speaking, biomarkers have applicability in disease diagnosis, prediction of treatment efficacy and of disease course, and even in prediction of disease onset in at-risk groups. Within neuroimaging, this could refer to anatomical volume changes, receptor expression patterns or electrophysiological signals, amongst others (Savitz et al., 2013). Whilst biomarkers of differential diagnosis, treatment efficacy and disease course would be useful to guide clinical decisions (Baskaran et al., 2012), this thesis focuses on biomarkers of prediction of recurrence in rMDD, so other biomarker types will not be discussed in detail. However, a recent review article (Savitz et al., 2013) states that, despite promising leads, “there are currently no brain

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\(^3\)In Stroop tasks, the participant is asked to name the ink colour of a word, rather than what it says. In emotional Stroop tasks, words of different valence are presented. It is thought that the participant has paid increased attention to the word itself if they take longer to name its colour (Dai and Feng, 2011).
imaging biomarkers that are clinically useful for establishing diagnosis or predicting treatment outcome in mood disorders”. The authors cite small effect sizes, and insufficient specificity and sensitivity.

Neuroimaging biomarkers of recurrence prediction in rMDD have received relatively little attention until recent years; in the fMRI literature, there are now a few studies of this type. There is a need to identify those most at risk of recurrence, as this could inform prophylactic treatment (Savitz et al., 2013).

The first study of this type compared brain activity during sad and neutral film clips. Elevated activation in the medial PFC during the sad condition was associated with recurrence risk, which they linked to rumination. The Stable Remission subgroup showed comparable activity to that of the HC group (Farb et al., 2011). A later study used a Go/No-Go task, and found reduced dorsomedial PFC activity in response to errors or negative feedback in the Recurring Episode subgroup relative to the Stable Remission and HC groups. The authors linked this result to maladaptive reappraisal of negative circumstances, although they conceded that this result required confirmation in a larger, medication-free group (Nixon et al., 2013). A third study did not split participants into Stable Remission and Recurring Episode subgroups. Instead, they correlated ventrolateral PFC signal during mood regulation (after sad mood induction) with Beck Depression Inventory (BDI) scores (Beck et al., 1988). They found lower signal at baseline correlated with higher subsequent symptom levels, as indicated by the BDI; this was linked to poor emotional regulation (Foland-Ross et al., 2013). Finally, a large study in school children with rMDD of pre-school-onset found that a smaller right anterior insula volume predicted likelihood of a subsequent MDE. Reduced insula volume was associated with the experience of pre-school pathological guilt (Belden et al., 2015).

All the above studies suffer, to varying degrees, from the confounding factor of psychotropic medication status. Such medications are known to affect brain structure and function (Savitz et al., 2013). With the exception of the Belden study, the sample sizes in the prospective studies were also no more than 16 participants per group, which raises concerns for the generalisability of the proposed biomarkers. A recent

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4 Go/No-Go tasks present two sets of stimuli. At any one time during the task, the participant is instructed to respond (i.e. ‘Go’) to one stimulus type and ignore (i.e. No-Go) the other stimulus type. Response typically involves button press, as in (Nixon et al., 2013).
study following on from the work by Green and colleagues (see Section 1.4.2 (Green et al., 2012)) was conducted on groups twice as large, which were also medication-free (Lythe et al., in press). In this study, self-blame-selective ATL- sgACC hyperconnectivity was found to distinguish participants who subsequently developed a recurring episode from those who remained in stable remission. The direction of this effect was unexpected, given the hypoconnectivity previously found to distinguish rMDD from HC participants (Green et al., 2012). The authors attributed this to the increased risk of recurrence in the more recent rMDD cohort (i.e. participants had more previous MDEs); the hypoconnectivity found previously could be a marker of resilience against recurrence rather than vulnerability (Lythe et al., in press). Other regions previously identified as showing functional disconnection with the ATL (e.g. the hippocampus (Green et al., 2012)) were not identified as having any predictive effects (Lythe et al., in press).

Biomarkers which help predict MDEs have the potential to be very valuable. However, those developed using fMRI are unlikely to be feasible for widespread use, especially given the high prevalence of MDD (Lopez et al., 2006). Although fMRI scanners are increasingly ubiquitous, their availability for use is often limited (Gabriel et al., 2015). fMRI is also an expensive technique due to both the machinery and associated running costs (Luck, 2014, Irani, 2011). In contrast, EEG is cheaper by many orders of magnitude both to buy and run (Luck, 2014). The equipment can be installed and run almost anywhere, and portable versions are also available (Gabriel et al., 2015). This means that availability would not be such a limiting factor as with fMRI. Biomarker development in EEG would be much more cost effective and feasible for widespread use. EEG also has fewer associated safety risks than fMRI, which has contraindications for some patients, e.g. those with pacemakers (Wager et al., 2007). Of course, there are spatial resolution limitations in EEG (Luck, 2014). These can be reduced in part by using a high density set-up for good scalp coverage. Also, source reconstruction techniques that integrate prior information about likely neural sources (e.g. from previous fMRI studies) also improve the accuracy of the EEG sources (Litvak et al., 2011). Even so, the resulting spatial resolution is not as high as fMRI, which is a disadvantage. However, EEG has a much higher temporal resolution than fMRI (Fabiani et al., 2007), so more closely reflects the speed of true neural activity. Also, EEG is a direct measure of
neural activity, believed to be summed post-synaptic potentials of synchronous neuronal patches (Pizzagalli, 2007, Fabiani et al., 2007). Conversely, fMRI is an indirect measure based on local haemodynamic changes associated with neural activity (Logothetis, 2003).

To the author’s knowledge\(^5\), there are currently no EEG studies of recurrence prediction in rMDD, and so studies within this thesis have been designed to fill that gap (see Chapters 3 and 4).

1.5 Neuropsychological findings in MDD

Impairments in symptomatic MDD have been demonstrated on a wide range of neuropsychological tasks, particularly on tasks probing affective cognition. This includes negative attentional biases, elevated feedback sensitivity and more negative perceptions when interpreting facial expressions; these findings are thoroughly reviewed in (Elliott et al., 2011, Roiser et al., 2011). This section will focus on findings in rMDD.

Many of the impairments seen in symptomatic MDD persist into remission (Elliott et al., 2011, Roiser et al., 2011). One of these impairments is in attentional bias, which has been displayed across a range of different tasks in rMDD. On an affective word judgement task, an rMDD group gave faster and more accurate responses to negative than positive words; this result was comparable to a current MDD group, but the HC group displayed the reverse pattern with a bias towards positive words (Atchley et al., 2003). Similarly, rMDD and symptomatic MDD groups have both displayed selective attention to sad compared to happy faces on a dot-probe task\(^6\); the opposite result was seen in the HC group (Joormann and Gotlib, 2007, Fritzsche et al., 2010). Additionally, adolescents who had recently had their first MDE were more accurate than an HC group in responding to sad words on an affective Go/No-Go task (Kyte et al., 2005). Attentional biases towards negative and/or away from positive stimuli

\(^5\)A search of the “Web of Science” database using keywords “depress*”, (“EEG” OR “electro*”), (“remitt*” OR “remiss*) and “predict*” was conducted. Resultant titles and abstracts were screened for relevance.

\(^6\)In a dot-probe task, pairs of stimuli (one neutral, one emotional) appear side by side on a screen. When the stimuli disappear, a dot appears in place of one of the stimuli. The participant presses a button to indicate where the dot is. It is thought that faster responses to dots that replace a certain stimulus type represents an attentional bias towards that stimulus type (Joormann and Gotlib, 2007).
seem to be fairly consistent in rMDD, although some research has only found differences from the HC group during sad mood induction (McCabe et al., 2000).

Facial emotion recognition tasks also highlight trait abnormalities in rMDD. Relative to an HC group, an rMDD group displayed increased ability to recognise fearful faces, but not anger, disgust, happiness or sadness. Interestingly, this ability normalised after intravenous citalopram administration, suggesting this result is specific to medication-free rMDD (Bhagwagar et al., 2004). In a study which included participants on medication, rMDD participants only had increased fear recognition rates relative to the current MDD group, not the HC group. However, the rMDD group recognised more angry and sad faces than both the other groups (Anderson et al., 2011). Recognition of neutral faces can also be affected. A symptomatic MDD group displayed slower and more inaccurate responses to neutral faces compared to an HC group, often categorising the neutral faces as sad or happy; this persisted after participants progressed into remission. However, they were not impaired on sad or happy face recognition (Leppänen et al., 2004). After sad mood induction, relative to HCs an rMDD group needed happy facial expressions to be more intense in order to identify them correctly; no group differences were seen for sad or angry faces (LeMoult et al., 2009). There is a more inconsistent pattern within the facial emotion recognition literature, which may be partly due to differences in medication status between studies. However, it is likely that there are impairments in facial emotion recognition in rMDD, which could impact on social interactions (Adolphs, 2002, Anderson et al., 2011).

1.5.1 Memory and MDD

Memory impairments in MDD are of particular interest in this thesis. This is due to the previously discussed finding (see Section 1.4.2) of a self-blame-selective functional ATL-hippocampus disconnection in rMDD when compared to an HC group. This was thought to represent reduced integration of specific autobiographical memory details whilst evaluating one’s own behaviour (Green et al., 2012).

Currently depressed individuals show a bias for remembering negative stimuli (Bradley et al., 1995, Dunbar and Lishman, 1984, Rinck and Becker, 2005) or a loss of the bias for remembering positive stimuli that is seen in HC groups (Gotlib et al., 2011, Harmer et al., 2009). Also, compared to an HC group, currently symptomatic
and rMDD groups both remembered more negative and fewer positive words that they had previously endorsed as self-referential; both biases were stronger in the current MDD group (Fritzsche et al., 2010). Memory impairment has been shown to increase with longer duration of past illness. The authors link this to cumulative neurotoxic effects on the hippocampus (Gorwood et al., 2008), which has previously been discussed in Section 1.4.1.

More specifically, MDD is associated with problems with autobiographical memory. Overgeneralisation of autobiographical memories (OGM) is when memories lose their temporal and situational context. For example, “I once spilled wine on a customer” might become “I was a terrible waitress”. Contextual information is needed to remain “autobiographically oriented within space and time” (Tulving 1984 in (Klimesch, 1999)). OGM is has been shown in both current MDD (Liu et al., 2013) and rMDD (Spinhoven et al., 2006). Such individuals retrieve fewer specific memories (Williams and Scott, 1988, Spinhoven et al., 2006, Nandrino et al., 2002) and are generally slower in their retrieval (Liu et al., 2013) when compared to HC groups. Even never-depressed participants with a first-degree family history of MDD, demonstrate increased OGM compared to those with no family history (Young et al., 2013); this suggests it is a vulnerability factor.

A valence bias in OGM has also been demonstrated in MDD. Early research showed that the responses of currently depressed participants to positive cues were less specific when compared to both negative cues and HC groups (Williams and Scott, 1988); positive responses are also slower compared to neutral (Gupta and Kar, 2012) or negative responses (Kaviani et al., 2005). This valence bias has been shown to persist in remission (Park et al., 2002, Gupta and Kar, 2012) and could conceivably precipitate or prolong a depressed state through reduced access to specific positive memories compared to negative ones. However, to the author’s knowledge, self-blame-related biases in memory have not been previously researched in the OGM literature. Given the guilt-selective ATL-hippocampal functional decoupling seen in rMDD (Green et al., 2012), it is important to study any distinction between self-blame- and valence-related biases.

Stressors, particularly early life stress (ELS), have also been associated with OGM (Crane et al., 2014, Hitchcock et al., 2014, Burnside et al., 2004). ELS predisposes to
hyper-responsiveness to stressful events later in life, leading to increased levels of circulating cortisol (Maniam et al., 2014). This could represent a common pathway for hippocampal damage and OGM in groups of people with ELS or MDD.

A widely used research tool in this field is the Autobiographical Memory Test (AMT) (Liu et al., 2013). The AMT tests recall of associative memory for autobiographical information in a specific temporal and spatial context. Participants are timed until they produce a specific autobiographical memory in response to a cue word (e.g. “happy” or “lonely”; (Williams and Scott, 1988)). In a previous PhD study, this task was adapted for the social neuroscience field to include positive and negative social concepts, such as “proud” and “angry” and administered to an rMDD and HC group (Green, 2011). There was no difference between the groups in time taken to recall a specific autobiographical memory to a negative cue word, but the rMDD group were faster than the HC group to positive cue words (Green, 2011). This result was unexpected and inconsistent with the literature, and requires further exploration. However, the AMT has been shown to correlate with measures of executive function (Dalgleish et al., 2007). Bearing this in mind, rather than using Green’s method in a larger rMDD group, a novel associative memory for social actions task was designed (see Section 2.4). This task probed associative memory for temporal and spatial context using manipulation of irrelevant contextual details in social action stimuli (see Chapter 6). Executive load was reduced through using a recognition memory approach (Kopelman and Stanhope, 1998, Haist et al., 1992). This task was balanced across conditions to allow separate investigation of both valence- and blame-related biases, without the confounding effects of executive load.

1.6 Aims

In summary, this thesis will study the involvement of self-blaming feelings in rMDD. Elevated self-blame is a common symptom of MDD, and has been consistently found to persist in rMDD (see Section 1.3.2). Neuroimaging studies (see Section 1.4) have found structural and functional changes in rMDD, some of which have been linked to this elevated self-blame; various moral cognitive neuroscience models have been built around these studies (see Section 1.3.3). The main model to be tested in this thesis is the EFEC model. This model states that the integration of fronto-temporo-mesolimbic network allows for the moral understanding of a given situation, prediction of possible consequences of actions and produces the
motivational feeling to act to produce the optimal outcome. The model states that failure to integrate the network would result in altered quality of feelings. Indeed, disruption in this network has been associated with elevated self-blame in rMDD. This model will be studied for the first time using EEG; compared with fMRI, EEG gives more temporal information, and is also more cost-effective to allow more feasible clinical transfer of any biomarkers developed. Self-blaming biases will also be studied in the context of associative memory biases; this has not been previously studied, and may be an important contributor to the persistence of elevated self-blame.

An rMDD and an HC group will be recruited in order to compare those at high- and low-risk for future depression, and therefore study vulnerability. The symptoms of the rMDD group will also be assessed at intervals during the following 14 months in order to establish “Stable Remission” and “Recurring Episode” subgroups; this means that predictive effects of study variables can be evaluated. The specific aims of this thesis, in chapter order, are as follows:

1. Chapter 3

Investigate self-blame-selective differences in the alpha and theta EEG bands of an rMDD group and an HC group. Increased theta has been consistently found in MDD, as has increased alpha, albeit less consistently (see Section 1.4.3). It could be argued that this reflects ongoing self-blaming processes, and so self-blame-selective increases in both the theta and alpha band are hypothesised in the rMDD relative to the HC group. Differences in the “Stable Remission” and “Recurring Episode” subgroups will also be explored; it is hypothesised that elevated self-blame-selective theta and alpha will distinguish the “Recurring Episode” subgroup from the “Stable Remission” and HC subgroups.

2. Chapter 4

Explore differences in self-blame-selective EEG sources in an rMDD group relative to an HC group; based on previous analyses (see Section 1.4.4), a self-blame-selective increase in sgACC activity was predicted in the rMDD group relative to the HC group. Additionally, differences in functional connectivity between the ATL and other brain areas will be investigated to contribute to knowledge of the temporal
dynamics of the EFEC model in rMDD. It was hypothesised that self-blame-selective ATL-sgACC hyperconnectivity would be seen in: 1) the rMDD group relative to the HC group; 2) those who developed a recurring episode relative to both those who remained in stable remission and the HC group.

3. Chapter 5

Across all participants, identify any correlation between separately collected self-blame-related fMRI and EEG source signals in regions of interest. It is hypothesised that activation in the two regions of interest (ATL and sgACC) will show correlation across the two modalities, when a time window encompassing semantic processing is selected from the EEG data.

4. Chapter 6

Investigate self-blame-selective contextual memory biases using a novel task for associative memory of social actions in an rMDD group compared to an HC group. Predictive effects of contextual memory biases will also be studied. The alternative models of self-blaming bias and negative emotionality will be tested, with the hypothesis that the rMDD group will show self-blame-selective rather than negative emotion-selective changes in associative memory when compared to the HC group. Specifically, it is hypothesised that, compared to the HC group, the rMDD group would show a reduced contextual memory for self-blame-selective scenarios compared to scenarios related to blaming others. This was based on the assumption that reduced contextual memory would increase proneness to overgeneralisation. It was also hypothesised that this self-blaming bias would be stronger in participants with early life stress and participants who subsequently developed another episode of depression.
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Chapter 2: General Methods

2.1 Participant recruitment procedure

Participants who took part in all the work which forms this PhD thesis were recruited as part of a larger UK Medical Research Council-funded\(^7\) project “Development of Cognitive and Imaging Biomarkers Predicting Risk of Self-Blaming Bias and Recurrence in Major Depression”. For an overview of recruitment and testing procedures, see Figure 2.1. A large cohort of participants with remitted major depressive disorder (rMDD) and healthy controls (HC) was recruited from July 2011 to October 2013.

Interested participants responded to online and print advertisements\(^8\) and were sent information about the study via e-mail. 707 potential participants gave oral consent to a 20-minute screening interview via telephone. This included questions about their psychiatric and general medical history and any treatments (see Appendix to this chapter for the telephone screening document; the original was written by Roland Zahn and Sophie Green, and further developed by Roland Zahn, Jennifer Gethin and Karen Lythe). The purpose of this interview was to increase likelihood that those invited for the clinical assessment would meet the study inclusion criteria, detailed in full below. Of the 707 who took part in the telephone screening interview, 276 were eligible and 202 of these were available and willing to be seen for the clinical assessment session (see Table 2.1 for full details of exclusion reasons). Clinical characteristics are given in each individual experimental chapter, as there is some variation in the specific participants included in each task and analysis.

\(^7\) Clinician scientist fellowship (G0902304) to Roland Zahn

\(^8\) Posters were placed in the local community (including university buildings, libraries and shops) and a print advertisement was placed in the Manchester Evening News; these advertisements recruited both rMDD and HC participants. Separate adverts for rMDD and HC participants were placed on the University of Manchester research volunteering website (http://www.studentnet.manchester.ac.uk/volunteer/). An additional Google advertisement was created to be displayed when depression-related terms were searched. This linked to the recruitment page of the study website (http://www.bbmh.manchester.ac.uk/blamebiases/takepart). The nature of the advert meant that more rMDD participants were recruited in this way, however some HC participants were recruited after seeing the Google advertisement.
**Figure 2.1 Study recruitment flow diagram** This details the recruitment and study process. The number of participants that took part in each stage is shown in brackets. Where timescales are not specified, these visits took place as soon as possible after the previous one. Timescales of follow-up visits are relative to the initial clinical assessment. Fully informed consent was taken prior to each study visit. Details of exclusion reasons are shown in Table 2.1. Some dropouts occurred at every stage where appointments could not be scheduled. Abbreviations: EEG, electroencephalography; fMRI, functional magnetic resonance imaging.
Table 2.1 Exclusion reasons for participants

Exclusions prior to the visit for electroencephalography and the associative memory for social actions task.

<table>
<thead>
<tr>
<th>Reason for exclusion</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Following telephone screening interview:</strong></td>
<td></td>
</tr>
<tr>
<td>Current antihypertensive medications or statins</td>
<td>20</td>
</tr>
<tr>
<td>Current antidepressant or other centrally active medications</td>
<td>52</td>
</tr>
<tr>
<td>Diabetes</td>
<td>4</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>5</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>3</td>
</tr>
<tr>
<td>Past cancer</td>
<td>7</td>
</tr>
<tr>
<td>Past stroke</td>
<td>1</td>
</tr>
<tr>
<td>Thyroid function problems</td>
<td>19</td>
</tr>
<tr>
<td>Vitamin D deficiency</td>
<td>1</td>
</tr>
<tr>
<td>Other psychiatric disorders than MDD</td>
<td>54</td>
</tr>
<tr>
<td>Substance or alcohol abuse</td>
<td>23</td>
</tr>
<tr>
<td>Other general medical condition</td>
<td>5</td>
</tr>
<tr>
<td>Family history of MDD/bipolar/schizophrenia (control group)</td>
<td>26</td>
</tr>
<tr>
<td>Excluded because of age-matching (control group)</td>
<td>3</td>
</tr>
<tr>
<td>Left-handed</td>
<td>20</td>
</tr>
<tr>
<td>Magnetic resonance imaging contraindications</td>
<td>77</td>
</tr>
<tr>
<td>Non-native English speaker</td>
<td>19</td>
</tr>
<tr>
<td>Out of age range</td>
<td>4</td>
</tr>
<tr>
<td>No reason recorded</td>
<td>5</td>
</tr>
<tr>
<td>Withdrawal after telephone screening interview</td>
<td>33</td>
</tr>
<tr>
<td>Not meeting full screening criteria for MDD</td>
<td>30</td>
</tr>
<tr>
<td>Had not been remitted from an episode for long enough</td>
<td>7</td>
</tr>
<tr>
<td>Fulfilled criteria for current MDD</td>
<td>13</td>
</tr>
<tr>
<td><strong>Total excluded after telephone screening interview</strong></td>
<td>431</td>
</tr>
<tr>
<td><strong>Following selection for initial assessment:</strong></td>
<td></td>
</tr>
<tr>
<td>Unable to schedule initial assessment</td>
<td>74</td>
</tr>
<tr>
<td>Fulfilled criteria for a bipolar disorder</td>
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<tr>
<td>Fulfilled criteria for current generalized anxiety disorder</td>
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</tr>
<tr>
<td>Fulfilled criteria for current social anxiety disorder</td>
<td>7</td>
</tr>
<tr>
<td>Magnetic resonance imaging contraindications</td>
<td>1</td>
</tr>
<tr>
<td>Did not meet full criteria for MDD</td>
<td>5</td>
</tr>
<tr>
<td>Had not been remitted from an episode for long enough</td>
<td>3</td>
</tr>
<tr>
<td>Fulfilled criteria for past substance abuse</td>
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</tr>
<tr>
<td>Probable personality disorder</td>
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<tr>
<td>Showed residual symptoms of post-traumatic stress disorder</td>
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<tr>
<td>Fulfilled criteria for current adjustment disorder</td>
<td>1</td>
</tr>
<tr>
<td>Fulfilled criteria for current MDD</td>
<td>1</td>
</tr>
<tr>
<td>Non-native English speaker</td>
<td>1</td>
</tr>
<tr>
<td>Fulfilled criteria for a past MDE that lasted for less than two months (control group)</td>
<td>1</td>
</tr>
<tr>
<td>Past depressive episode that did not fulfill criteria for past MDE (control group)</td>
<td>1</td>
</tr>
<tr>
<td>Probable or definite positive first degree family history of MDD (control group)</td>
<td>4</td>
</tr>
<tr>
<td>Withdrawal after the first assessment</td>
<td>1</td>
</tr>
<tr>
<td>Enrolled onto study prior to introduction of this visit into the study</td>
<td>16</td>
</tr>
<tr>
<td>Unable to schedule this visit</td>
<td>27</td>
</tr>
<tr>
<td>Excluded because of age-matching for this visit (control group)</td>
<td>6</td>
</tr>
<tr>
<td>Unexpected neurological abnormality detected after MRI scan</td>
<td>1</td>
</tr>
<tr>
<td>Skin condition (unsuitable for electroencephalography)</td>
<td>1</td>
</tr>
<tr>
<td>Braided hair (unsuitable for electroencephalography)</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total excluded from this session after selection for initial assessment</strong></td>
<td>169</td>
</tr>
</tbody>
</table>

707 participants consented to the telephone screening interview. After exclusions, 107 participants (71 rMDD, 36 HC) completed the electroencephalography visit. 83 (55 rMDD, 30 HC) also completed the associative memory for social actions task, which was introduced later. Abbreviations: HC, healthy control; (r)MDD, (remitted) major depressive disorder; MDE, major depressive episode.
The clinical assessment session determined whether each participant met the full inclusion criteria. A clinical history was taken, including: past and current medications, neurological and other physical symptoms, interpersonal relationship history and stressful life events. The following modules from the Structured Clinical Interview-I (SCID-I) for Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (First et al., 2002) were administered to assess psychiatric history: mood episodes, psychotic and associated symptoms, substance use disorders, anxiety disorders and eating disorders and the Global Assessment of Functioning (GAF) scale. The GAF assesses social and occupational functioning (First et al., 2002).

A series of standard questionnaires was completed for each participant: Montgomery-Åsberg Depression Rating Scale (MADRS; (Montgomery and Åsberg, 1979)) to quantify past and current depressive symptoms; Weissman Family History Screen (shortened version; (Weissman et al., 2000)) to assess first-degree family history; Longitudinal Interval Follow-up Evaluation baseline assessment (LIFE; shortened version; (Keller et al., 1987)) to assess psychosocial functioning. The Addenbrooke’s Cognitive Examination was also administered to participants aged over 50 years to exclude cognitive impairments (Mioshi et al., 2006). Those conducting the assessments had completed appropriate training with the instruments used. Inter-rater reliability for the SCID-I past MDD diagnosis was high: κ=0.64 (KL & RZ) and κ=1 (KL & JG) (Zahn et al., 2015a).

All participants were also assessed with a phenomenological psychopathology-based interview (AMDP; see Appendix to this chapter) translated with permission from the original German edition (Faehndrich and Stieglitz, 2007, Faehndrich and Stieglitz, 1997) by a native German speaker (RZ) and checked by a native English speaker (Sophie Green). This interview rated past and current individual symptoms on a four-point scale (from absent to severe). These ratings determined the MADRS and GAF scores and also provided evidence for diagnosis.

As part of the clinical assessment session, almost all participants were seen by a consultant psychiatrist (RZ) who confirmed the diagnoses of the assessors (JG or KL); if unable to be seen by RZ, the assessor discussed the diagnosis in full with RZ afterwards.
For inclusion, all participants: were aged between 18 and 65 years, were right-handed, had normal or corrected-to-normal vision and had English as their sole or dominant first language. To be included in the rMDD group, participants had at least one past major depressive episode (MDE) as defined by DSM-IV, which was also moderate or severe as defined by the International Classification of Diseases (ICD-10, World Health Organization). The MDE was not secondary to another psychiatric or general medical condition, lasted at least two months and was fully remitted for six months or more.

Exclusion criteria for all participants were: contraindications for a functional magnetic resonance imaging (fMRI) scan; a MADRS score above 10, the threshold for depression (Zimmerman et al., 2004); current self-harming behaviour; poor psychosocial functioning, a marker of either incomplete remission or personality disorder; current axis-I disorder (American-Psychiatric-Association, 2000) or residual symptoms of one. Additionally, a history of any of the following: bipolar disorder, schizophrenia, schizo-affective disorder, substance or alcohol abuse as defined by the SCID-I; a learning or developmental disability, neurological or physical disorder that substantially impacted on psychosocial or brain function. Finally, current centrally active medication (except hormonal contraceptives) was an exclusion criterion. This was ruled out by self-report and urine drug screen at the clinical assessment visit. Common excluded medications included antidepressants, antipsychotics and antihistamines, and common acceptable medications included non-centrally active analgesics (e.g. paracetamol and ibuprofen) and antispasmodics (e.g. mebeverine).

Additionally, HC participants were excluded if they had a history of any axis-I disorder (American-Psychiatric-Association, 2000) with a corresponding category in ICD-10, or had used antidepressant or antipsychotic medications. Those with a first-degree family history of MDD, bipolar disorder or schizophrenia were also excluded.

Study inclusion/exclusion criteria can also be found in previously published work (Zahn et al., 2015a). Table 2.1 details the exclusion reasons up to the electroencephalography (EEG) and memory session, as this forms the major part of data collection presented in this thesis. A summary table of inclusion/exclusion criteria can also be found in the Appendix to this Chapter.
Such thorough inclusion/exclusion criteria enabled exclusion of many confounding variables from this study, most notably centrally active medications, which are often found in imaging studies of psychiatric populations (e.g. (Nixon et al., 2013)); antidepressants are known to affect activation patterns in functional imaging studies (Delaveau et al., 2011). The criteria also ensured that the key variable of interest, vulnerability to an MDE, could be examined; the HC and rMDD groups were at low and high risk respectively.

Once a participant met inclusion criteria for the study, they attended an fMRI session, where they completed a social action judgement task in the scanner and subsequently rated the stimuli outside of the scanner (see Section 2.2). In a separate session, they completed the same task during EEG (see Section 2.3) and an associative memory task without EEG (see Section 2.4). At the start of each session, the participant was asked if they had had any mood or energy changes to ensure they were still in remission, and any medication changes were noted.

Participants were then contacted at three intervals in the 14 months following their initial clinical assessment. Participants were also asked to contact the study team if they experienced a recurrence of symptoms at any other time point. After three months, the LIFE (Keller et al., 1997) was administered via telephone to identify any relevant mood changes; if such changes were clinically significant, the participant was seen for a full assessment. Full follow-up assessments also occurred at six and 14 months. These involved a psychiatric exam similar to the baseline clinical assessment. The LIFE interview was administered, which identified any periods of low mood, which were then assessed using the SCID-I. If participants met criteria for an MDE, this visit was the end of their participation in the study. The MADRS was also administered. A 14 month follow-up period was chosen as the recurrence risk in an medication-free rMDD group is approximately 50% in this time period (Viguera et al., 1998); for the prospective study, it was desirable to have approximately equal numbers of participants with and without a recurrence for group comparisons\(^9\). Of those who took part in the EEG session, six participants could not be scheduled to complete the follow-up stage of the study.

\(^9\) In this way, rMDD and HC participants were recruited in a 2:1 ratio, so that there were approximately equal numbers in HC, Stable Remission and Recurring Episode groups.
Participants were reimbursed for their time and travel costs for the sessions they completed. This research study was approved by the South Manchester NHS Research Ethics Committee (reference number: 07/H1003/194).

2.2 Value-related moral sentiment task

Data from this task are discussed in Chapters 3-5.

The value-related moral sentiment task (VMST) was the main task used in this PhD. It is a 180-item social action judgement task designed to explore neurocognitive correlates of moral emotions associated with blaming the self and others. Each stimulus is a short sentence describing an action between the participant and their best friend (using the participant and their best friend’s real names). In the version used here, the action is always counter to accepted social norms, e.g. “Paul [the participant] acts bossily towards Ian [his best friend]”. All sentences take this form, with a negative or negated positive action. The words describing social actions were selected based on previous normative studies (Zahn et al., 2007, Zahn et al., 2009c). In half the stimuli (n = 90), the participant is the agent and the best friend is the recipient. In the other half, the roles are reversed but the rest of the sentence remains identical, e.g. “Ian acts bossily towards Paul”; this ensures that both conditions are equally balanced in terms of verbal working memory load, syntax and semantics. Stimuli are presented in a pseudorandom order across three experimental runs. This task has previously enabled detection of self-blame related functional disconnections in an rMDD group relative to an HC group in an fMRI study (Green et al., 2012), so is suitable for addressing the aims of this PhD.

For this PhD, the majority of participants completed the VMST in an fMRI scanner and then later during EEG. Whilst undergoing imaging, it is unfeasible to ask participants to make many ratings about each sentence, so they were asked only whether the statement made them feel “mildly unpleasant” or “very unpleasant” (button press response); further ratings were made directly after the fMRI scan. Participants were asked to rate each sentence for unpleasantness on a 7-point Likert scale, and to select the feeling that they most associated with the behaviour from the following list: guilt, contempt/disgust towards oneself, anger/indignation towards oneself, shame, contempt/disgust towards best friend, anger/indignation towards best friend, no feeling or other feeling. Participants did not complete these additional
ratings after the EEG, as they were assumed to be stable over time. Such subjective ratings allowed imaging trials to be categorised for each participant individually, to ensure that only trials relevant to the hypotheses were analysed. Previous fMRI research (Pulcu et al., 2014a, Green et al., 2012) contrasted feelings associated with moral transgressions such as guilt, shame and indignation. However, more trials per condition are required for EEG analyses to increase signal-to-noise ratio (Yesilyurt et al., 2010), so to avoid high levels of participant exclusion due to insufficient trials, self- and other-agency were contrasted instead. However, only trials rated as highly intensely unpleasant were contrasted, as these can be assumed to be evoking self- or other-blame related feelings; these are superordinate categories of feelings such as guilt and indignation. These two conditions of interest will be termed “self-blame” and “other-blame” throughout. For each participant in each agency condition, a median split based on the unpleasantness rating was used to select these trials (trials rated as the median or above, or >1 if the median was 1).

Although the stimuli used in the EEG were identical to the previous and current fMRI studies, the VMST was adapted for use in EEG (see Figure 2.2). The stimulus presentation time was shortened from 5 to 2.2 seconds to account for the improved temporal resolution of EEG compared to fMRI (Luck, 2014). Stimulus sentences were shortened to allow them to be read faster e.g. “Paul bossy Ian”, with each word being displayed on a separate line vertically stacked; this also reduced saccadic eye movements. To avoid confusion, it was explained to participants beforehand that this style of stimulus had the same meaning as the fMRI scan version. A specific response window (2 seconds) followed each stimulus to avoid motor artifacts during stimulus presentation. Given the reduced inter-trial interval, a distraction task in the form of a simple calculation was added after each stimulus; this was to ensure participants were not attending to the previous stimulus during presentation of the subsequent one. A null fixation condition was added directly before each stimulus rather than pseudo-randomly distributed throughout each experimental run to allow for EEG baseline subtraction as standard.
Figure 2.2 Value-related moral sentiment task schematic An example self-agency trial from the EEG version.

2.3 Electroencephalography

EEG data are discussed in Chapters 3-5.

2.3.1 Acquisition

Whilst participants completed the VMST, EEG was recorded at 512 Hz with a 64-electrode ActiveTwo system and Actiview acquisition software (BioSemi, Amsterdam, Netherlands). EEG electrode placement followed the 10-20 International System (Pizzagalli, 2007). In Biosemi systems, the ground electrode is replaced with one active and one passive electrode; they form a feedback loop to drive the common mode voltage of the participant as close as possible to the analog-to-digital converter reference voltage (the amplifier “zero”). Full details can be found at http://www.biosemi.com/faq/cms&drl.htm. Four external electrodes measured the horizontal and vertical electrooculogram; these were placed at the outer canthus of each eye and above and below the right eye.
2.3.2 Preprocessing

Brain Electrical Source Analysis 5.2 (BESA GmbH, Gräfelfing, Germany) was used for initial data preprocessing. Artifacts from vertical and horizontal eye movements were identified and removed using a threshold of ± 100 µV. A high-pass filter of 1 Hz (forward phase shift, 6 dB/octave) was applied to remove low-frequency drift. Faulty channels were restored by interpolation of the signal from neighbouring channels; this applied to nine participants for one channel and two participants for two channels. Data were exported to MATLAB 7.14 (MathWorks, Natick, Massachusetts) in epochs of -500 to 2200 ms peri-stimulus time and baseline correction was conducted using the 100 ms immediately prior to stimulus presentation. The final 100 ms of the fixation baseline was selected to minimise movement artifacts from a button press immediately prior to the fixation.

Preprocessing was completed within the MATLAB toolbox Statistical Parametric Mapping 8 (SPM8; http://www.fil.ion.ucl.ac.uk/spm/). Any trial which reached the threshold of ± 80 µV within the critical peri-stimulus time window of -200 to 1500 ms was rejected, along with any channel in which ≥20% of total trials were artifactual. After artifact removal, participants with fewer than 30 trials remaining in either the self- or the other-blame condition were excluded from analyses (2 rMDD and 2 HC). This ensured signal to noise ratio was sufficient to detect the evoked signal (Saddy and Beim Graben, 2002). Finally, data were re-referenced to the average over the scalp electrodes, hereafter referred to as the average reference.

2.3.3 Time window selection

For each participant, a condition average was computed using robust averaging within SPM8. This technique gives an artifactual activity score to each sample in each trial, and then every sample is weighted by this score during the averaging process; highly artifactual trials are downweighted and vice versa (Litvak et al., 2011).

In order to objectively select time windows of interest for analysis, global field power (GFP) was calculated in MATLAB. GFP is a measure of signal variance over time (Clementz et al., 2007) collapsed across all electrodes, conditions and participants (irrespective of group). Three peaks were seen: 100-300 ms, 300-400 ms and 400-700 ms (see Figure 2.3).
This identifies the time windows with the most variance in the data (across all electrodes, conditions and participants). It is used to define the time windows for further analysis (see Chapters 3-5).

To study differences in neural correlates of emotional judgements related to the meaning of self- and other-blame-related stimuli from the VMST (see Section 2.2), a time window encompassing semantic processes was chosen. In the EEG literature, the marker most associated with semantics is the N400, which typically peaks around 400 ms post-stimulus presentation (Kutas and Federmeier, 2011). Transcranial magnetic stimulation at this time point has also been shown to selectively disrupt semantic processing (Jackson et al., 2015). However, semantic effects have been shown much earlier (Hauk et al., 2012). This suggests the 300-400 ms time window as most appropriate, as it contains the well-established peak of semantic processing, but also captures earlier activity that may also reflect semantic processing. The other time windows were investigated in a time-frequency analysis (see Chapter 3), but 300-400 ms was the focus of this thesis.

2.3.4 Source analysis

Source analysis data are presented in Chapters 4 and 5.

Locating the sources of EEG data is a mathematically ill-posed problem, as there are infinite source solutions to any given scalp data (Pizzagalli, 2007); there are fewer electrodes than neural sources. However, the best solution can be computed and evaluated using modelling approaches. The steps are summarised in Figure 2.4.

Source reconstruction was conducted in SPM8. Solutions for all participants were computed simultaneously to avoid sources being so focal at an individual level that there was no overlap at the group level (Litvak et al., 2011). A model of the inner
skull, outer skull and scalp was generated from the SPM8 template MRI scan; a head model defines the electromagnetic conductive properties of the head for use in model calculations (Pizzagalli, 2007). It was originally the intention to use each individual participant’s MRI scan, collected as part of the larger study, however the field of view did not cover the whole skull and so unfortunately could not be used for this purpose. A cortical mesh of normal resolution (8196 vertices) was also generated; these vertices define possible sources of EEG activity (Litvak et al., 2011). Co-registration, where the EEG electrode positions are plotted onto the structural MRI scan (Litvak et al., 2011), was conducted using five EEG electrode positions as fiducials (Iz, FPz, Cz, T7 and T8). The forward model was then computed; this is a calculation of the effect of every cortical dipole on each electrode (Litvak et al., 2011). This was completed using a Boundary Elements Model, a head model which takes into account the different conductive properties of head tissues including the skin, skull and cerebrospinal fluid (Pizzagalli, 2007); the output is a “lead field matrix” containing the effect of every vertex in the cortical mesh on each EEG electrode (Litvak et al., 2011).

During the inverse reconstruction step, where the most likely sources are calculated based on the EEG data and forward model, both conditions were inverted together to allow for valid statistical comparison of the resultant images (Litvak et al., 2011). A greedy search multiple sparse priors algorithm was used, in which combinations of sources are iteratively processed until the optimal solution, the closest fit to the observed data, is found (Ashburner et al., 2013). Source priors were also included to improve the solution: a thresholded statistical mask created from the fMRI data of 106 participants (37 HC and 69 rMDD; see Appendix to this chapter). This mask was the combination of blood-oxygen-level dependent one-sample t contrasts self-blame > fixation and other-blame > fixation, added together using the SPM8 function ImCalc. The mask therefore represented both conditions and participant groups. Both contrasts were inclusively masked and thresholded at $p = 0.005$ (uncorrected) with an extent threshold of 4 voxels. The benefit of using priors is that they are only incorporated into the solution if they improve the fit of the model (Litvak et al., 2011). Evoked power between 1 and 50 Hz was localised at 300-400 ms, the main time window of interest. This process was completed for each
participant at the level of both the condition average, for use in standard statistical analyses, and single trials, for use in psychophysiological interaction analyses.
**Head model:** the three layers of the inner skull, outer skull and scalp are shown in different shades of red. The cortical surface is shown in blue.

**Co-registration:** the 64 EEG electrodes were plotted on the scalp. Blue circles represent those that were used as fiducials (Iz, FPz, Cz, T7 and T8); their co-ordinates were specified. Green circles represent the remaining electrodes, whose positions were inferred from the fiducials.

**Forward model:** the effect of every cortical dipole on each electrode was calculated. In this schematic, the yellow circle represents one source (of 8196). The arrows represent the effect of this source on two (of 64) electrodes. This process was repeated until an 8196 x 64 lead field matrix was created.

**Inverse model:** the lead field matrix (effects of the sources on the electrodes) was compared with the observed EEG data. Combinations of sources were iteratively processed until the optimal solution (the sources which generate the closest fit to the observed data) was found.

**Result:** best fit of sources are shown on a glass brain.

**Figure 2.4 Source analysis pipeline schematic** Figures a, b and e are examples of the steps produced using SPM8. Figures c and d are schematics produced using Microsoft PowerPoint.
2.3.5 Psychophysiological interaction analysis

*Psychophysiological interaction analyses are presented in Chapter 4.*

A psychophysiological interaction (PPI) analysis was conducted to investigate condition-related differences in the functional connectivity of a seed region and other brain regions (Friston et al., 1997). The seed co-ordinate, \(x = 58, y = -4, z = -4\) (co-ordinates are given in Montreal Neurological Institute [MNI] space), was selected based on an analysis of sources across all participants and conditions (see Figure 2.5); a 2 x 2 full factorial model was used with the following factors: condition (self- and other-blame) and group (rMDD and HC). The selected co-ordinate was the peak of the cluster which was most centrally located within the right anterior superior temporal area, an area known to be involved in processing of social concepts (Zahn et al., 2007, Zahn et al., 2009c).

**Figure 2.5 Psychophysiological interaction analysis seed region** Axial, coronal and sagittal views of the seed co-ordinate, which is circled in red \((x = 58, y = -4, z = -4\) [MNI co-ordinates]). Blue areas denote all regions activated across participants and conditions in a 2 x 2 full factorial model of the EEG source data (factors: group [rMDD and HC] and condition [self- and other-blame]). Image is thresholded at \(p < 0.05\) (family-wise error-corrected).

The three variables required for the PPI analysis were calculated in MATLAB: ‘xn’, the seed signal (using an 8 mm sphere around the seed co-ordinate), ‘PSY’, the psychological condition (i.e. self- or other-blame) and ‘PPI’, the product of \(xn\) and \(PSY\), which shows the effect of the psychological condition on the physiological signal. For each participant, a multiple regression model using all three variables was
run; this enabled creation of contrasts to compare functional connectivity between the seed region and other brain regions in the two different conditions. Smoothing of the contrast images at 10 mm was conducted to increase spread of focal activations. These smoothed contrast images were taken to the group level for statistical analysis to identify group differences in connectivity with the seed region in one condition relative to the other.

2.4 Associative memory for social actions task

Data from this task are presented in Chapter 6.

Following on from a previous PhD study discussed in Chapter 1.5.1 (Green, 2011), the associative memory for social actions task was designed to probe specific memories associated with social interactions in more depth. In addition to positive and negative conditions, it was decided that the task would benefit from self- and other-agency conditions, in order to study memory for blaming and praising behaviours associated with the self and others.

Instead of modifying the Autobiographical Memory Test (see section 1.5.1), novel non-autobiographical stimuli put into a personal context were designed. This was to enable modification of irrelevant contextual details to probe spatial and temporal memory specificity across the different conditions.

Stimuli for the associative memory task were adapted from previous responses to a Social Scenario Generation Task. These responses were collected from 28 healthy participants at the Cognitive Neuroscience section, National Institute of Neurological Disorders and Stroke, National Institutes of Health in Bethesda, Maryland (Green et al., 2013a). Participants in this task were asked to generate examples of specific social behaviours in response to positive and negative social concepts (e.g. “generous” or “bossy”) and moral sentiments (e.g. “shame”). An example of a response to the “embarrassment” cue was: “During a party, a guest at the party spilled wine on the host’s carpet”.

From the resultant scenarios, 40 that were most appropriate to be adapted for the current task were selected; such sentences needed to involve two individuals, and be realistic positive or negative interactions between two close friends. Scenarios were then adapted to be actions between the participant and their best friend, involving a
specific time or location. Two versions of each scenario were created: one where the participant was the agent of the action (self-agency), and one where the best friend was the agent (other-agency). These sentences were identical with the exception of agency and an irrelevant contextual detail (the specific time or location of the action). Of the 40 sentences in each agency condition, half were positive and half were negative, giving four conditions: self-praise, other-praise, self-blame and other-blame. Working memory load was balanced across conditions as the number of words was equal.

The above example from the Social Scenario Generation Task was adapted into stimuli for the current task as follows (also see Appendix to this chapter for full stimuli):

“At your party, Paul spilled wine on your lounge carpet” (other-blame; best friend Paul is the agent, participant is the recipient)

“At Paul’s party, you spilled wine on their landing carpet” (self-blame; participant is the agent, best friend Paul is the recipient)

The stimulus presentation time was set to 6 seconds; this has previously been shown to be ample time to read and fully understand a sentence of similar length (Moll et al., 2007). Participants were given 3 seconds to rate the valence (“good”/ “bad”) after seeing each sentence; this was to aid their concentration throughout the task. Following their response, a fixation cross was presented for any remaining time.

Ideally, participants would not have known this was a memory task until the retrieval phase in order to prevent them employing memory techniques not true to everyday life. However, piloting indicated that the task was too difficult without this knowledge given the number of stimuli. It was important to keep the number of stimuli high for increased statistical power, so participants were told in advance that they were doing a memory task. However, they were not told specifically which aspect of the stimuli they would be tested on.

The gap between encoding and retrieval was set at 60 minutes. During this time, the participants completed other tasks; the exact time interval was recorded and factored into analyses, as small variations across participants were inevitable and this could have had an effect on their ability to remember the stimuli.
To allow specificity of associative memory to be tested in the retrieval phase, half the stimuli (equally distributed across conditions) were modified; an irrelevant detail, the time or the place was changed. These foil sentences, along with the 40 unchanged stimuli were presented again at the same pace as before (see Figure 2.6). After each sentence, participants were given 3 seconds to make a forced choice (“yes”/“no”) about whether they had seen that particular sentence before. It was made clear prior to the retrieval phase that foil sentences would only be subtly different from sentences they had seen before. Following their response, a fixation cross was presented for any remaining time. A recognition memory approach was used to minimise executive demands that are known to confound performance on specific memory tasks such as the AMT (Dalgleish et al., 2007).

Response time and accuracy were chosen as outcome measures so that speed-accuracy trade-off difference between groups and conditions could be explored.

**Figure 2.6** Associative memory for social actions task schematic An example self-praise trial from the retrieval phase.
Appendix (Chapter 2)

The telephone screening document used in the initial stage of participant recruitment (see section 2.1).
Screening ID No: S __ __ __

Instructions for Interviewer are marked in bold.
Text to be read literally is put into quotation marks and “italic”

Oral consent to be read first
(this is the ethics approved wording which cannot be changed):

"I would like to do a short phone interview with you which will take around 15 minutes. This is necessary to see whether some conditions rule out that we can include you into the study. You will be asked questions about psychiatric, neurological and medical symptoms, treatments, learning problems and whether such symptoms have occurred in your family. I will also ask about substance or alcohol abuse. Things which are an obstacle to participate in MRI studies such as possible pregnancy or metallic objects will also be asked. Results of these questions will not be stored, but we ask your permission to store your contact information and whether you passed the screening for the study group in an electronic database which is protected by a password and can only be accessed by the investigators."
<table>
<thead>
<tr>
<th>Question</th>
<th>Response</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do you agree to this interview?</td>
<td>yes</td>
<td>If no =&gt; Exclusion</td>
</tr>
<tr>
<td>How many years of education have you had?</td>
<td></td>
<td>towards the end of the study, controls will be selected to be age- and education- matched to the patient population</td>
</tr>
<tr>
<td>What is your age?</td>
<td></td>
<td>If &lt; 18 =&gt; Exclusion If &gt; 65, exclusion for study 2</td>
</tr>
<tr>
<td>Are you right-handed?</td>
<td>yes</td>
<td>If no =&gt; Exclusion</td>
</tr>
<tr>
<td>Is English your first language?</td>
<td>yes</td>
<td>If no =&gt; Exclusion If any other early languages mentioned/foreign accent detected - Is English your parents’ first language? At what age did you first speak English? Which language did you speak at home/school?</td>
</tr>
<tr>
<td>Are you currently taking any medications?</td>
<td>yes</td>
<td>If current centrally active medications that will not be stopped anyway for other reasons than study participation before participation =&gt; Exclusion</td>
</tr>
<tr>
<td>If yes -&gt; What medications?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have you ever, at any time, taken anti-depressant or anti-psychotic medications (such as Prozac, Zoloft, Zyprexa, Haldol)?</td>
<td>yes</td>
<td>If yes =&gt; Exclusion as Healthy control</td>
</tr>
<tr>
<td>Have you ever been diagnosed with or treated for any psychiatric or psychological problem (for example: Depression, Bipolar or manic-depressive, Anxiety, Posttraumatic Stress, Eating, Borderline Personality, Obsessive-Compulsive, Psychotic or Schizophrenic disorders, Attention-Deficit-Disorder)?</td>
<td>yes</td>
<td>If yes =&gt; Exclusion as Healthy control If more than 1 =&gt; did they occur independently? If other symps occurred during MDD then potentially RMD group If yes =&gt; who diagnosed? Anxiety Disorders allowed in MDD groups if not prominent.</td>
</tr>
<tr>
<td>Question</td>
<td>Answer</td>
<td>Answer</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>--------</td>
<td>--------</td>
</tr>
<tr>
<td>Have you ever been diagnosed with or treated for any neurological problem (weakness, gaze problems, walking problems, motor coordination, epilepsy, stroke, parkinson’s)?</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Have you ever had a drug or alcohol problem?</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Have any of your first degree relatives (parents, siblings or children) ever been treated for or diagnosed with psychosis, schizophrenia, depression, bipolar disorder or manic depression?</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Have you ever had any significant physical health problems, for example heart, lung problems, diabetes, hypertension, arterial diseases, thyroid function problems, liver, kidney disorders, rheumatoid disorders, infectious diseases or anything else?</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Have you ever had any learning disabilities?</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Do you have hearing problems or problems with vision?</td>
<td>yes</td>
<td>no</td>
</tr>
</tbody>
</table>
Adapted MINI (Lecrubier et al., 1997) screening questions for all participants

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Have you ever been consistently depressed or down, most of the day, nearly every day, for at least 2 weeks?</td>
<td>yes</td>
<td>no</td>
<td>If yes =&gt; Exclusion as Healthy control, check eligibility for MDD groups</td>
</tr>
<tr>
<td>Have you ever had 3 or more alcoholic drinks within a 3 hour period on 3 or more occasions?</td>
<td>yes</td>
<td>no</td>
<td>If yes =&gt; Explore further with question below</td>
</tr>
<tr>
<td>Have you ever taken any drugs more than once: for example stimulants, amphetamines, diet pills, cocaine, morphine, LSD, “mushrooms”, “ecstasy”, cannabis (“hash”), tranquilizers, steroids, sleep pills or pain killers?</td>
<td>yes</td>
<td>no</td>
<td>If yes =&gt; Explore further (eg. When drugs were last taken, how often, check participant is likely to be drug free for study, mention drug screening in study)</td>
</tr>
<tr>
<td>In the past have you been intoxicated, high, or hungover from alcohol or drugs when you had other responsibilities (work, school, home) or did you have legal problems, problems with other people or accidents because of this?</td>
<td>yes</td>
<td>no</td>
<td>If yes or questionable =&gt; explore further Ask for examples of behaviour, how frequently this occurred, any significant consequences If significant =&gt; Exclusion</td>
</tr>
</tbody>
</table>
**Screening questions for all participants**

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Have you ever had a phase of at least 2 weeks in your life where you needed only a few hours (for example 3h) of sleep and were still totally alert and very active the whole day, where you were very enthusiastic and did things you usually wouldn’t do?</td>
<td>yes</td>
<td>no</td>
<td>If yes =&gt; Exclusion</td>
</tr>
<tr>
<td>For the next question, please just say “yes” or “no”, no details will be asked nor recorded. Have you ever been traumatized in a way, that you feared your life was in danger or were you sexually assaulted?</td>
<td>yes</td>
<td>no</td>
<td>If yes =&gt; Are you still bothered by it? If yes =&gt; Do you avoid anything (eg. places/people) because of this? – Exclusion if currently significantly distressed</td>
</tr>
<tr>
<td>Do you experience frequent states of tension and use self-injuries such as cutting or burning to reduce tension?</td>
<td>yes</td>
<td>no</td>
<td>If yes =&gt; Exclusion</td>
</tr>
<tr>
<td>Do you get very tense or anxious, when your personal things (i.e. on your desk) are not symmetrically arranged, when you can’t wash your hands, after you have touched a door knob, when you can’t perform certain daily activities according to a fixed and detailed routine (e.g. washing, certain professional or household activities)?</td>
<td>yes</td>
<td>no</td>
<td>If yes =&gt; Did this only occur during depressive phases? Does this interfere with your professional or personal life?</td>
</tr>
<tr>
<td>Have you ever heard voices with no person or audio-device as a source?</td>
<td>yes</td>
<td>no</td>
<td>If yes =&gt; Exclusion</td>
</tr>
<tr>
<td>Have you ever lost control of your body movements or your thoughts and felt controlled by an external power?</td>
<td>yes</td>
<td>no</td>
<td>If yes =&gt; Exclusion</td>
</tr>
<tr>
<td>Have you experienced unusual signs referring specifically to you and indicating great danger, for example by a group or person threatening your life?</td>
<td>yes</td>
<td>no</td>
<td>If yes =&gt; Exclusion</td>
</tr>
</tbody>
</table>
**History of Depression group only (study 2)**

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>When was your last depressive phase?</td>
<td></td>
<td></td>
<td>&gt; 6 months well to be included</td>
</tr>
<tr>
<td>When did you start to feel well again?</td>
<td></td>
<td></td>
<td>only included if yes (sometimes minimal or mild symptoms, but not significantly distressing or interfering, then see on day 1)</td>
</tr>
<tr>
<td>Do you now feel as well as before your first depressive phase and do you feel back to your normal self?</td>
<td>yes</td>
<td>no</td>
<td>only included if yes</td>
</tr>
<tr>
<td>In your most severe depressive phase, have you been consistently depressed or down, most of the day, nearly every day, for at least 2 months?</td>
<td>yes</td>
<td>no</td>
<td>only included if yes</td>
</tr>
<tr>
<td>During the most severe period of that depressive episode, did you have a general loss of drive and energy, where your activities were either slowed down or only possible against a huge inner resistance?</td>
<td>yes</td>
<td>no</td>
<td>only included if yes</td>
</tr>
<tr>
<td>During the most severe period of that depressive episode, did you lose almost completely your ability to enjoy nearly everything?</td>
<td>yes</td>
<td>no</td>
<td>only included if yes</td>
</tr>
<tr>
<td>During the most severe period of that depressive episode, did you lose your ability to respond to things that previously gave you pleasure, or cheered you up?</td>
<td>yes</td>
<td>no</td>
<td>only included if yes</td>
</tr>
</tbody>
</table>
Eligibility for MRI studies to be completed for all participants

| For women: Are you absolutely sure that you are not pregnant? | yes | no | exclusion for MRI if no |
| Do you have permanent eyeliner or other permanent make-up? | yes | no | potential exclusion for MRI if yes because of reduced image quality |
| Do you have loose dental implants such as fillings or crowns which cannot be removed before scanning? | yes | no | absolute exclusion for MRI if yes |
| Do you have any implanted electrical devices? (pacemaker, brain stimulator, ear implants, implanted delivery pumps) | yes | no | exclusion for MRI if yes |
| Could you have any metal in your body? (metal clips on the wall of a large artery, metallic prostheses including metal pins and rods, heart valves, shrapnel fragments) | yes | no | exclusion for MRI if yes |
| Have you ever worked as a welder or metal worker? (this can lead to small metal fragments in the eye which you may be unaware of) | yes | no | exclusion for MRI if yes |
| Do you get anxious in confined spaces? | yes | no | exclusion for MRI if yes |
| Do you require a hearing aid? | yes | no | exclusion for MRI if yes |

If eligible get date-of-birth and address – record on a separate piece of paper, not this document.

Interview is stopped as soon as exclusion criterion is detected, the interviewer apologizes for not being able to include the person and thanks again for the willingness to participate. If necessary, one can explain that it is important for research studies to focus on specific types of depression, because otherwise it is difficult to find significant results if patients with different types of depression or other problems are mixed together.

If person meets all inclusion/exclusion criteria for one of the study groups (healthy control or history of MDD), contact information and study group are stored in password protected excel sheet. The PIS and Consent for the respective study is sent to the person after screening and an appointment for day 1 is scheduled with at least 24 h time after the person has received the PIS and signed the consent.

This sheet is reviewed after the phone interview, exclusion reasons are coded in separate sheet not linked with screening-ID, the questionnaire is then shredded.

Comment: The screening questions for major psychiatric disorders are based on clinical experience as providing high sensitivity and specificity for bipolar disorder, schizophrenia, OCD, PTSD and Borderline Personality Disorder. The screening questions for inclusion into MDD groups were taken from the melancholic subtype questions of the MINI/SCID. This is because melancholic subtypes are most likely to fulfil ICD-10 severe depressive episode criteria and score high enough on the MADRS.

The AMDP interview

1-2 characteristic questions for all self-observation based symptoms were translated from a German symptom rating interview (Faehndrich and Stieglitz, 2007) by Roland Zahn and checked by a native speaker (Sophie Green) for comprehensiveness.

2 English translations of the symptom labels and numbers correspond to the original version (Faehndrich and Stieglitz, 1997). Instructions for ratings are based on these definitions.
## Phenomenological Psychopathology

*Depression-typical Disorders of Formal Thought, Affect, Drive and Psychomotility* | Circadian D., Sleep & Appetite

### Prompt questions during semi-structured clinical interview

<table>
<thead>
<tr>
<th>Prompt</th>
<th>S</th>
<th>O</th>
<th>Comments/Qualitative description</th>
<th>Quantitative classification</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inhibited Thinking (15)</strong></td>
<td>S</td>
<td>O</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Does it feel like the brakes have been put on your thinking, or your thinking is hindered, like against a resistance?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Retarded Thinking (18)</strong></td>
<td>O</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Restricted Thinking (18)</strong></td>
<td>O</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[If patient returns to one central topic and cannot be driven to talk about neutral topics (e.g., hobbies, leisure)]</td>
<td>O</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Rumination (20)</strong></td>
<td>S</td>
<td>O</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Do you feel compelled to think about certain things over and over again? Does this disturb you, do you find this unpleasant?</td>
<td>S</td>
<td>O</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Feeling of loss of feeling (60)</strong></td>
<td>S</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Has anything changed in the way you feel? Can you describe this further?</td>
<td>S</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Are you able to be sad or happy? Or do you rather feel empty inside?</td>
<td>S</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Do you have the impression that your feelings have become numb or stony (feeling empty inside, dead, rigid)?</td>
<td>S</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Blunted Affect (61)</strong></td>
<td>O</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Felt loss of vitality (62)</strong></td>
<td>S</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• In general, how do you feel physically?</td>
<td>S</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Do you have the feeling that your liveliness, your momentum, your vigour have diminished? Do you feel rather downcast, weak, worn out or tired?</td>
<td>S</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Depressed mood (63)</strong></td>
<td>S</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• How would you describe your mood at the moment?</td>
<td>S</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Are you sad? Do you feel down?</td>
<td>S</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hopelessness (64)</strong></td>
<td>S</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• How do you feel about the future? Can you imagine that everything will get better again?</td>
<td>S</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety (65)</td>
<td>S</td>
<td>absent</td>
<td>mild</td>
<td>medium</td>
</tr>
<tr>
<td>----------------------</td>
<td>-------</td>
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</tr>
<tr>
<td>Are you more anxious than usually, [if yes], can you give an example?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Are you anxious, because you expect that something terrible could happen?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Feelings of inadequacy (71)</th>
<th>S</th>
<th>absent</th>
<th>mild</th>
<th>medium</th>
<th>severe</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>How is your self-confidence and self-esteem?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do you think that you do not succeed in the same way as you used to?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do you sometimes think that you are worth less than other people?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Feelings of guilt (73)</th>
<th>S</th>
<th>absent</th>
<th>mild</th>
<th>medium</th>
<th>severe</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is there anything that you feel self-reproach for?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do you worry to have done something wrong? [examples]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Feelings of anger</th>
<th>S</th>
<th>Towards Self = 1, Other = 2, Both = 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do you sometimes feel angry?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is this mostly towards yourself or others, or both?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>What are typical situations?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>How often and how much bothering?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do you get physically aggressive or do you shout?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Feelings of contempt/disgust</th>
<th>S</th>
<th>Towards Self = 1, Other = 2, Both = 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do you sometimes feel disgust, contempt, hate, or loathing?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Which term would you prefer?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is this mostly towards yourself or others, or both?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>What are typical situations?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>How often and how much bothering?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do you get physically aggressive or do you shout?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Feelings of shame or guilt</th>
<th>S</th>
<th>Relevance: Guilt = 1, Shame = 2, Both(equal) = 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Which is more relevant, are these the same or different?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>What are typical situations?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>How often and how much bothering?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Connection between moral feelings</th>
<th>S</th>
<th>Agree on best model with participant:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Considering the experience of the following feelings you have mentioned (list all of the ones reported from: “low self-worth”, “guilt”, “shame”, “anger”, “contempt/disgust/hate/loathing towards self or towards others”)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Which is the one most bothering you?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>What do you think is the connection between those feelings, do you think one causes the other?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mark the type of connection between feelings:

- $\rightarrow$ causal one direction = 1 (e.g. 1st to 2nd)
- $\leftarrow$ causal other direction = 2 (e.g. 2nd to 1st)
- $\leftrightarrow$ causal bidirectional = 3
- Independent = 4
- About equally bothering
<table>
<thead>
<tr>
<th>Condition</th>
<th>S</th>
<th>O</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delusions of guilt (42)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Same prompt question as for feelings of guilt [examples]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Affective lability (77)</td>
<td>S</td>
<td>O</td>
</tr>
<tr>
<td>- Have you noticed that your mood changes very rapidly, going up and down, and that you have no control over this?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Affective rigidity (79)</td>
<td>O</td>
<td></td>
</tr>
<tr>
<td>Lack of drive (80)</td>
<td>S</td>
<td>O</td>
</tr>
<tr>
<td>- How is your energy, drive, initiative?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Addition (if diminished): is this also the case for things you enjoy to do? [ask for example]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inhibition of drive (81)</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>- Do you need more energy than usual for everything, as if you are working against a resistance?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Addition (if yes): is this also the case for things you really want to do? [ask for example]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor restlessness (83)</td>
<td>S</td>
<td>O</td>
</tr>
<tr>
<td>- Is it hard for you to sit still in one place?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worse in the morning (89)</td>
<td>S</td>
<td>O</td>
</tr>
<tr>
<td>- Do you feel worse in the morning than in the evening?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social withdrawal (92)</td>
<td>S</td>
<td>O</td>
</tr>
<tr>
<td>- Do you avoid the company of other people more often than usual?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interrupted sleep (102)</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>- Can you describe how you are sleeping at the moment?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- After you fall asleep, are you able to sleep right through or do you wake up again in between?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early waking (104)</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>- When do you wake up in the morning? Is this earlier than usual?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Can you then fall asleep again?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite (106)</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>- How is your appetite at the moment? Do you enjoy eating?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

S=Self-observation based, O=Other (Clinician, Caregiver)-observation based, Questions can be slightly reworded and order is not fixed. Psychopathological assessment is based on the patient’s description and the clinician’s observation but the clinician has to ask free follow-up questions to get enough detail to be able to interpret the response. N/A = not applicable, because symptom cannot be assessed with certainty. Assessment rules for severity and presence/absence are described in ^2
## Summary of inclusion/exclusion criteria

<table>
<thead>
<tr>
<th>Group</th>
<th>Inclusion</th>
<th>Permitted</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Both</strong></td>
<td>Aged 18-65 years (inclusive)</td>
<td>-</td>
<td>Aged &lt;18 or &gt;65 years</td>
</tr>
<tr>
<td><strong>Both</strong></td>
<td>Right-handed</td>
<td>-</td>
<td>Left-handed</td>
</tr>
<tr>
<td><strong>Both</strong></td>
<td>Normal vision</td>
<td>Corrected-to-normal vision</td>
<td>Vision which could not be corrected</td>
</tr>
<tr>
<td><strong>Both</strong></td>
<td>English as first language</td>
<td>Brought up bilingual, with English as the dominant first language</td>
<td>English not first language Brought up bilingual, but English was not the dominant language</td>
</tr>
<tr>
<td><strong>rMDD</strong></td>
<td>≥1 past MDE: -meeting SCID criteria -lasting ≥ 2 months -fully remitted ≥ 6 months</td>
<td>-</td>
<td>Past depressive symptoms: -not meeting SCID criteria -lasting &lt;2 months -secondary to other psychiatric or general medical condition -not remitted for ≥ 6 months</td>
</tr>
<tr>
<td><strong>Both</strong></td>
<td>-</td>
<td>Hormonal contraceptives Non-centrally active medications e.g. ibuprofen</td>
<td>Centrally-active medications e.g. antidepressants, antipsychotics, antihistamines, benzodiazepines</td>
</tr>
<tr>
<td><strong>Both</strong></td>
<td>-</td>
<td>Past self-harming behaviour</td>
<td>Current self-harming behaviour</td>
</tr>
<tr>
<td><strong>Both</strong></td>
<td>-</td>
<td>-</td>
<td>Current or residual symptoms of an axis-I disorder</td>
</tr>
<tr>
<td><strong>rMDD</strong></td>
<td>-</td>
<td>History of an eating disorder or anxiety disorder</td>
<td>History of bipolar disorder, schizophrenia, schizo-affective disorder</td>
</tr>
<tr>
<td><strong>Both</strong></td>
<td>-</td>
<td>Permitted to use alcohol, but not &lt;24 hours before study appointments</td>
<td>History of substance or alcohol abuse Current use of drugs of abuse e.g. cannabis</td>
</tr>
<tr>
<td><strong>Both</strong></td>
<td>ACE score &gt;88 (only over 50s tested)</td>
<td>-</td>
<td>ACE score ≤ 88</td>
</tr>
<tr>
<td><strong>Both</strong></td>
<td>-</td>
<td>-</td>
<td>Physical disorder that significantly impacts on psychosocial/neurological function e.g. diabetes</td>
</tr>
<tr>
<td><strong>Both</strong></td>
<td>-</td>
<td>Dyslexia not requiring special schooling</td>
<td>Learning/developmental disability that significantly impacts on psychosocial/neurological function e.g. autism</td>
</tr>
<tr>
<td>Both</td>
<td>-</td>
<td>-</td>
<td>Neurological disorder e.g. epilepsy, past stroke, multiple sclerosis</td>
</tr>
<tr>
<td>-------</td>
<td>---</td>
<td>---</td>
<td>-------------------------------------------------------------------</td>
</tr>
<tr>
<td>HC</td>
<td>-</td>
<td>-</td>
<td>History of any axis-I disorder</td>
</tr>
<tr>
<td>HC</td>
<td>-</td>
<td>Second degree family history of MDD, bipolar disorder or schizophrenia</td>
<td>First degree family history of MDD, bipolar disorder or schizophrenia</td>
</tr>
<tr>
<td>HC</td>
<td>-</td>
<td>-</td>
<td>Past use of antidepressant or antipsychotic medications</td>
</tr>
</tbody>
</table>

Abbreviations: ACE, Addenbrooke’s Cognitive Exam; HC, healthy control; (r)MDD, MADRS, Montgomery-Åsberg Depression Rating Scale; MDE, major depressive episode; (remitted) major depressive disorder; SCID, structured clinical interview for DSM-IV
Source analysis mask

Below is the thresholded statistical mask that was used as source priors to improve the source solution (see Section 2.3.4). This mask was created from the fMRI data of 106 participants (37 HC and 69 rMDD). It was the combination of blood-oxygen-level dependent one-sample t contrasts self-blame>fixation and other-blame>fixation, added together using ImCalc. Both contrasts were inclusively masked and thresholded at $p = 0.005$ (uncorrected) with an extent threshold of 4 voxels. The mask is shown from MNI co-ordinates $x = 0, y = 0, z = 0$. 
**Associative memory for social actions task**

All 80 stimuli for the encoding phase of the task are listed below, broken down by condition (other-blame, self-blame, other-praise, self-praise). “[BESTFRIEND]” was replaced with the participant’s best friend’s first name.

The line below each stimulus shows how it was changed for the retrieval phase. 50% of the stimuli in each condition remained the same (indicated by “no change”); 50% of the stimuli in each condition had an irrelevant contextual detail changed, and became a foil (the word changed is indicated by an asterisk).
Other-blame condition

1. When driving your car at 1am*, [BESTFRIEND] fell asleep and hit a tree
   *3am
2. At your party, [BESTFRIEND] spilled wine on your lounge* carpet
   *hall
3. When with your boss in the canteen* [BESTFRIEND] spoke very badly about you
   *office
4. After you won a competition yesterday evening, [BESTFRIEND] spread untrue rumours about you
   *(no change)
5. At your games evening one Wednesday*, [BESTFRIEND] cheated during a poker game
   *Friday
6. When babysitting in your house, [BESTFRIEND] slapped your child
   *(no change)
7. Last summer*, you lent money to [BESTFRIEND] and they did not pay it back
   *autumn
8. In front of strangers in The Red Lion*, [BESTFRIEND] brought up one of your private memories
   *The White Horse
9. When talking about politics last Monday, [BESTFRIEND] disrespected your opinions
   *(no change)
10. In an afternoon* meeting, [BESTFRIEND] took all the credit for your effort
    *evening
11. During some important assessments in the exam hall, [BESTFRIEND] plagiarised your work
    *(no change)
12. In your kitchen*, [BESTFRIEND] stole money from your wallet
    *lounge
13. Whilst you were away on holiday in May*, [BESTFRIEND] kissed your long-term partner
    *July
14. When with other friends in the Arndale Centre, [BESTFRIEND] could not keep your secret
    *(no change)
15. At a Saturday night dinner party, [BESTFRIEND] took your slice of cake
    *(no change)
16. After a double date at Cineworld cinema, [BESTFRIEND] criticised your choice of partner
    *(no change)
17. On the morning of your birthday, [BESTFRIEND] acted sick to avoid your party
    *(no change)
18. To avoid seeing you last Tuesday, [BESTFRIEND] lied about their plans
    *(no change)
19. After too much alcohol, [BESTFRIEND] yelled at you in Queens Park*
    *Heaton Park
20. In their garden, after noticing their phone was missing, [BESTFRIEND] wrongly accused you of stealing it
    *(no change)
Self-blame condition

1. When driving [BESTFRIEND]'s car at 2am*, you fell asleep and hit a tree
   *4am
2. At [BESTFRIEND]'s party, you spilled wine on their landing* carpet
   *bedroom
3. When with [BESTFRIEND]'s boss in the lift*, you spoke very badly about them
   *corridor
4. After [BESTFRIEND] won a competition yesterday morning, you spread untrue
   remarks about them
   *(no change)*
5. At [BESTFRIEND]'s games evening one Tuesday*, you cheated during a poker game
   *Thursday
6. When babysitting in your garden, you slapped [BESTFRIEND]'s child
   *(no change)*
7. Last spring*, [BESTFRIEND] lent money to you and you did not pay it back
   *winter
8. In front of strangers in The King's Arms*, you brought up one of [BESTFRIEND]'s
   private memories
   *The Royal Oak
9. When talking about politics last Wednesday, you disrespected [BESTFRIEND]'s
   opinions
   *(no change)*
10. In a lunchtime* meeting, you took all the credit for [BESTFRIEND]'s effort
    *morning
11. During some important assessments in the school library, you plagiarised
    [BESTFRIEND]'s work
    *(no change)*
12. In [BESTFRIEND]'s conservatory*, you stole money from their wallet
    *bedroom
13. Whilst [BESTFRIEND] was away on holiday in June*, you kissed their partner
    *August
14. When with other friends in the Trafford Centre, you could not keep [BESTFRIEND]'s
    secret
    *(no change)*
15. At a Friday night dinner party, you took [BESTFRIEND]'s slice of cake
    *(no change)*
16. After a double date at Odeon cinema, you criticised [BESTFRIEND]'s choice of partner
    *(no change)*
17. On the afternoon of [BESTFRIEND]'s birthday, you acted sick to avoid their party
    *(no change)*
18. To avoid seeing [BESTFRIEND] last Monday, you lied about your plans
    *(no change)*
19. After too much alcohol, you yelled at [BESTFRIEND] in Tatton Park*
    *Gorton Park
20. In your car, after noticing your phone was missing you wrongly accused
    [BESTFRIEND] of stealing it
    *(no change)*
Other-praise condition

1. When people gossiped about you in the reception at work, [BESTFRIEND] defended you
   *(no change)*
2. When you were ill one Friday night, [BESTFRIEND] left a party early to look after you
   *(no change)*
3. When you were homeless over Christmas, [BESTFRIEND] offered you a spare bed
   *(no change)*
4. When you were unemployed last summer, [BESTFRIEND] paid your debts
   *(no change)*
5. After a serious illness last summer*, [BESTFRIEND] donated a kidney to you
   *winter
6. In the afternoon meeting, [BESTFRIEND] let you take credit for their work
   *(no change)*
7. On a cold December* day, [BESTFRIEND] gave you their coat
   *January
8. After the loss of a loved one, [BESTFRIEND] comforted you on a bench
   *(no change)*
9. When you fell in to Lake Coniston*, [BESTFRIEND] jumped in to save you
   *Windermere
10. After a long flight home, [BESTFRIEND] picked you up from Gatwick* airport
    *Stansted
11. When you attended a funeral one Saturday, [BESTFRIEND] did all your housework for you
    *(no change)*
12. At 2am* one morning, [BESTFRIEND] bailed you from jail
    *4am
13. In the office, [BESTFRIEND] shared their lunch with you
    *(no change)*
14. When you were in a rush, [BESTFRIEND] offered you a lift to Asda*
    *Morrisons
15. So you could visit your parents in Salford Royal* Hospital, [BESTFRIEND] looked
    after your pet dog
    *Stepping Hill
16. After your haircut, [BESTFRIEND] complimented your appearance in a wine lounge
    *(no change)*
17. One morning*, when you fell over, [BESTFRIEND] helped you get up
    *evening
18. After you were fired, [BESTFRIEND] took you to dinner at a Chinese restaurant
    *(no change)*
19. When you lost your wallet on holiday in France*, [BESTFRIEND] lent you some
    money
    *Spain
20. To give you a night off one Tuesday*, [BESTFRIEND] looked after your children
    *Thursday
Self-praise condition

1. When people gossiped about [BESTFRIEND] in the canteen at work, you defended them
   (no change)
2. When [BESTFRIEND] was ill one Saturday night, you left a party early to look after them
   (no change)
3. When [BESTFRIEND] was homeless over Easter, you offered them a spare bed
   (no change)
4. When [BESTFRIEND] was unemployed last winter, you paid their debts
   (no change)
5. After a serious illness last autumn*, you donated a kidney to [BESTFRIEND]
   *spring
6. In the morning meeting, you let [BESTFRIEND] take credit for your work
   (no change)
7. On a cold February* day, you gave [BESTFRIEND] your coat
   *November
8. After the loss of a loved one, you comforted [BESTFRIEND] on a sofa
   (no change)
9. When [BESTFRIEND] fell in to Lake Grasmere*, you jumped in to save them
   *Ullswater
10. After a long flight home, you picked [BESTFRIEND] up from Luton* airport
    *Heathrow
11. When [BESTFRIEND] attended a funeral one Sunday, you did all their housework for them
    (no change)
12. At 3am* one morning, you bailed [BESTFRIEND] from jail
    *1am
13. In the car, you shared your lunch with [BESTFRIEND]
    (no change)
14. When [BESTFRIEND] was in a rush, you offered them a lift to Sainsbury's*
    *Tesco
15. So [BESTFRIEND] could visit their parents in Manchester Royal Infirmary*, you looked after their pet dog
    *Royal Preston Hospital
16. After [BESTFRIEND]’s haircut, you complimented their appearance in a cocktail bar
    (no change)
17. One afternoon* when [BESTFRIEND] fell over, you helped them get up
    *night
18. After [BESTFRIEND] was fired, you took them to dinner at an Italian restaurant
    (no change)
19. When [BESTFRIEND] lost their wallet on holiday in Germany*, you lent them some money
    *Belgium
20. To give [BESTFRIEND] a night off one Wednesday*, you looked after their children
    *Monday
References (Chapter 2)


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Chapter 3: Sustained increase in theta power during self-blame in remitted major depression

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JG adapted an existing task for use with EEG, with advice from RZ and WE. JG completed all EEG data collection and analyses, with advice from RZ and WE. KL conducted all fMRI data collection and analyses. JG, KL, CW and RZ were all involved in participant recruitment and clinical assessments. WE, KL and RZ made helpful comments on the manuscript.
3.1 Abstract

Abnormalities in the theta and alpha frequency bands during resting electroencephalography (EEG) have been found in major depressive disorder (MDD). We investigated the role of self-blame, a common and distressing symptom of MDD which persists into remission, in theta and alpha changes. Sixty-seven medication-free participants with remitted MDD (rMDD) and 33 healthy controls with no personal or family history of MDD completed a task designed to evoke feelings related to blaming the self and others, whilst EEG was recorded. Group differences were detected only in the theta band; a three-factor interaction between group, blame condition and post-stimulus time was found. This was due to the rMDD group showing a self-blame-selective increase in power, which decreased less over time, relative to the HC group. A composite score representing the condition and time interaction showed negative correlation with a measure of self-hate (subscale of the Interpersonal Guilt Questionnaire), a maladaptive form of self-blame. This composite score also correlated positively with right dorsolateral prefrontal cortex (dLPFC) activity from functional magnetic resonance imaging data using the same task. We speculate that altered temporal dynamics of theta rhythms contribute to dysfunctional integration of contextual information in the dLPFC, thereby contributing to the overgeneralisation of self-blaming emotions.
3.2 Introduction

The potential for electroencephalography (EEG) to detect individual differences in psychological state was first discussed in 1936 (Lemere, 1936). Since then, much research using EEG to investigate abnormalities in psychiatric disorders, including major depressive disorder (MDD), has been published. To date, the most consistent findings in MDD have been observed at rest in the theta and alpha frequency bands (Olbrich and Arns, 2013). In order to link such EEG signals to MDD symptoms, the present study used a task designed to evoke emotions related to blaming the self and others.

Elevated resting theta power has been found to distinguish MDD patients from healthy controls (HC) in a large study (Grin-Yatsenko et al., 2010). Possible generators of increased theta have been identified in the frontal cortex (Arns et al., 2015, Korb et al., 2008), rostral anterior cingulate cortex (rACC) (Arns et al., 2015, Korb et al., 2008) and the subgenual (sg)ACC (Jaworska et al., 2012); the latter is associated with guilt in MDD (Green et al., 2012, Zahn et al., 2009c), and is a target site for deep brain stimulation in treatment-refractory MDD (Mayberg et al., 2005). Deep brain stimulation to the sgACC is thought to act via alterations in limbic-cortical circuit activity (Mayberg et al., 2005); given the supposed role of theta in synchronisation of distributed brain areas (O’Neill et al., 2013, Klimesch, 1999, Jones and Wilson, 2005), increased sgACC theta could also be a marker of disruption in this network.

Elevated resting alpha power has also been found in MDD across multiple scalp areas including frontal (Jaworska et al., 2012), parietal (Jaworska et al., 2012, Grin-Yatsenko et al., 2010) and occipital (Grin-Yatsenko et al., 2010) sites. Frontal alpha asymmetry has also been extensively investigated after early influential work found increased left prefrontal alpha activity in MDD (Henriques and Davidson, 1991) and also remitted MDD (rMDD) (Henriques and Davidson, 1990) compared to an HC group; increased alpha was interpreted as hypoactivation leading to “deficits in the approach system”, which is associated with anhedonia (Henriques and Davidson, 1991). However, many studies have since failed to replicate their findings (Carvalho et al., 2011, Gold et al., 2013, Reid et al., 1998, Segrave et al., 2011). The prominent Henriques and Davidson study has since been criticised for group differences being
driven by a few individuals (Olbrich and Arns, 2013). The involvement of alpha in MDD therefore remains unclear.

Cross-sectional studies contribute to the understanding of the pathophysiology of MDD, however there is increasing interest in predictive biomarkers. EEG is particularly suited to this, as its relatively low cost and high availability (Olbrich and Arns, 2013, Luck, 2014) make clinical transfer more feasible. Most studies focus on prediction of treatment response, with the aim of improving the “trial-and-error” approach to treatment selection (Baskaran et al., 2012). Source methods have consistently shown that increased pre-treatment theta in the rACC (Brodmann area [BA] 24/32) at rest predicts a positive response to various antidepressant treatments (Korb et al., 2009, Mulert et al., 2007, Pizzagalli et al., 2001). This theta increase also correlates with increased glucose metabolism (Pizzagalli et al., 2003); increased rACC activity is consistently associated with positive treatment outcome across imaging modalities (Pizzagalli, 2011), so is a promising biomarker. However, more recent research suggests that an individual’s history of treatment failure may influence the value of this biomarker (Arns et al., 2015).

Whilst prediction of treatment response is clearly important, a marker of vulnerability in an rMDD group would also be of value; there is a need to identify those most at risk of recurrence, as this could inform prophylactic treatment (Savitz et al., 2013). The current study was completed by an rMDD and HC group to investigate vulnerability to depression rather than the state of depression (Bhagwagar and Cowen, 2008); the rMDD group also completed a longitudinal phase of the study to investigate predictive effects on clinical course.

Given the evidence of involvement of theta and alpha in MDD, we elected to explore these frequency bands in the context of self-blame rather than at rest. Excessive self-blaming emotions are a recognised symptom of MDD (First et al., 2002), and biases towards blaming the self, relative to others, persist into remission (Zahn et al., 2015a). We predicted that there would be differences between the rMDD and HC groups on self-blame-related power in both theta and alpha frequency bands. We also hypothesised that these differences would distinguish between those who remained in stable remission and those who had a major depressive episode within the longitudinal study period.
3.3 Method

3.3.1 Participants
Potential participants responded to advertisements, in both print and online media, for the UK Medical Research Council-funded project “Development of Cognitive and Imaging Biomarkers Predicting Risk of Self-Blaming Bias and Recurrence in Major Depression”. After receiving full information about the study, 707 participants gave oral consent to an initial screening interview via telephone. Suitable participants gave written informed consent and were assessed by a senior psychiatrist (RZ) and with the Structured Clinical Interview-I for DSM-IV (First et al., 2002). For inclusion in the rMDD group, participants had at least one major depressive episode of two-month duration, had been in remission for at least six months and were free from centrally-active medication (except hormonal contraceptives). They also had no current co-morbid or relevant past axis-I disorders. For the HC group, participants had no personal or first-degree family history of MDD. For full details of inclusion and exclusion criteria and recruitment procedures, see Chapter 2.1, including Table 2.1 which details exclusion reasons up to and including the EEG part of the study. The recruitment procedure is also documented in the Supplemental Materials of previous work (Zahn et al., 2015a). Participants were reimbursed for their time and travel costs. This research study was approved by the South Manchester NHS Research Ethics Committee (reference number: 07/H1003/194).

As part of this larger study, 71 rMDD and 36 HC participants completed a social action judgement task whilst EEG was recorded. Of these, 7 participants were excluded from analyses: n = 1, neurological abnormality on magnetic resonance imaging scan; n = 2, fulfilled criteria for current depression at EEG session; n = 4 insufficient trials for analysis after artifact removal (<30 trials per condition).

67 rMDD and 33 HC participants were included in the final analysis. The two groups did not differ on years of age (rMDD: median 36, range 18-64, HC: median 27, range 20-64, $U = 930, p = 0.198$), years of education (rMDD: median 17, range 12-22, HC: median 17, range 14-25, $U = 900, p = 0.127$), or gender (rMDD: 48 females, HC: 22 females, $X^2 = 0.261, p = 0.610$). The Global Assessment of Functioning (GAF) Scale (First et al., 2002) showed that the HC group had higher levels of social and occupational functioning and lower symptom levels (rMDD: median 90, range...
70-90, HC: median 90, range 81-90, \( U = 651.5, p < 0.001 \). However, all participants had no more than mild symptoms or functioning problems. All participants also had Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery and Åsberg, 1979) scores below the threshold for depression (<10 points), but the rMDD group showed a trend for higher scores (rMDD: median 0, range 0-6, HC: median 0, range 0-4, \( U = 919, p = 0.086 \)).

The rMDD participants were also followed up for 14 months after the initial clinical assessment. This created two “prospective” rMDD subgroups: those who remained in “Stable Remission” \( (n = 31) \) and those who had a “Recurring Episode” \( (n = 20) \). Some participants \( (n = 10) \) developed significant symptoms, but did not reach the threshold for a major depressive episode, so are not included in the prospective analysis. These participants had a Psychiatric Status Rating (Keller et al., 1987) of 4, or 3 if treatment was required. Six participants did not complete the follow-up phase of the study, and so are also not included in the prospective analysis. The Stable Remission and Recurring Episode groups did not differ on years of age, years of education, gender, GAF score or MADRS score (see Table 3.1).

### Table 3.1 Demographics of Stable Remission and Recurring Episode groups

<table>
<thead>
<tr>
<th></th>
<th>Stable Remission</th>
<th>Recurring Episode</th>
<th>Statistic</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>39 (20-63)</td>
<td>37 (18-64)</td>
<td>( U = 293.5 )</td>
<td>0.750</td>
</tr>
<tr>
<td>Education (years)</td>
<td>17 (14-22)</td>
<td>17 (12-20)</td>
<td>( U = 233.5 )</td>
<td>0.134</td>
</tr>
<tr>
<td>Gender</td>
<td>22 F, 9 M</td>
<td>12 F, 8 M</td>
<td>( X^2 = 0.658 )</td>
<td>0.417</td>
</tr>
<tr>
<td>MADRS score</td>
<td>0 (0-4)</td>
<td>0 (0-6)</td>
<td>( U = 282.5 )</td>
<td>0.538</td>
</tr>
<tr>
<td>GAF score</td>
<td>90 (70-90)</td>
<td>85.5 (70-90)</td>
<td>( U = 249.5 )</td>
<td>0.205</td>
</tr>
</tbody>
</table>

Data are shown in the format: median (range). F = female, M = male.

All participants also completed the same task during a functional magnetic resonance imaging (fMRI) scan. 21 participants were subsequently excluded from any analyses involving fMRI data: \( n = 10 \), signal dropout; \( n = 6 \), excessive head movement on fMRI; \( n = 5 \) incomplete fMRI data. 50 rMDD and 29 HC participants were included in analyses involving fMRI data.

#### 3.3.2 Value-related moral sentiment task

The value-related moral sentiment task (VMST) is a 180-item social action judgement task designed to explore neural correlates of moral emotions associated with blame attribution. Each stimulus is a short sentence describing an action between the participant and their best friend. The action is always counter to
accepted social norms, in either negative or negated positive form, e.g. “Tara [the participant] acts stingily towards Willow [her best friend]”. In half the stimuli ($n = 90$), the participant is the agent and the best friend is the recipient. In the other half, the roles are reversed but the rest of the sentence remains identical, e.g. “Willow acts stingily towards Tara”; both conditions are balanced on verbal working memory load, syntax and semantics. Stimuli were taken from previous normative studies (Zahn et al., 2007, Zahn et al., 2009c).

Both the fMRI and the EEG sessions used the same stimuli in a pseudo-random order over three counterbalanced runs, but stimulus presentation was adapted for each modality (see also Chapter 2.2). In fMRI, stimuli were presented for up to 5 seconds, during which participants made a button press response on whether the sentence made them feel “mildly unpleasant” or “very unpleasant”\textsuperscript{10}; following their response, a fixation cross was presented for any remaining time. A jittered inter-trial interval of mean duration 4 seconds (range: 2-6 seconds) followed. A null fixation condition ($n = 90$ trials) was mixed in amongst the stimulus trials. In EEG, stimuli were presented for 2.2 seconds, as EEG has a higher temporal resolution (Luck, 2014). To allow stimuli to be read in this time, the sentences were presented in a shortened form (e.g. “Tara stingy Willow”; see Figure 3.1). Stimuli were followed by a designated response window (2 seconds) to avoid motor artifacts during stimulus presentation. A simple calculation was added after each stimulus as a distraction, given the shortened inter-trial interval. The null fixation condition was added before each stimulus to allow for baseline subtraction, as is standard in EEG analysis.

After the fMRI session, participants rated each sentence for unpleasantness on a 7-point Likert scale. These subjective ratings allowed trials from both imaging modalities to be categorised for each participant individually. The present study analysed trials related to self-blame and other-blame only; this was assumed to be trials which were rated as highly intensely unpleasant (trials rated as the median or above, or >1 if the median was 1) in the self- and other-agency conditions respectively.

\textsuperscript{10} “Mildly unpleasant” and “very unpleasant” were the only options during fMRI and EEG recordings. More detailed unpleasantness ratings for each stimulus were taken after the fMRI scanning session, using a 7-point Likert scale (1: not unpleasant, 7: very unpleasant)
Figure 3.1 VMST schematic  An example self-agency trial from the VMST; presentation times are shown below each screen

3.3.3 EEG acquisition
EEG was recorded at 512 Hz with a 64-electrode ActiveTwo system and Actiview acquisition software (BioSemi, Amsterdam, Netherlands). EEG electrode placement followed the 10-20 International System (Pizzagalli, 2007). In Biosemi systems, the ground electrode is replaced with one active and one passive electrode; they form a feedback loop to drive the common mode voltage of the participant as close as possible to the analog-to-digital converter reference voltage (the amplifier “zero”). Full details can be found at http://www.biosemi.com/faq/cms&drl.htm. Four external electrodes measured the horizontal and vertical electrooculogram; these were placed at the outer canthus of each eye and above and below the right eye.

3.3.4 EEG preprocessing
Brain Electrical Source Analysis 5.2 (BESA GmbH, Gräfelfing, Germany) was used for the following preprocessing steps: removal of artifacts from vertical and horizontal eye movements (threshold ± 100 µV); 1 Hz high-pass filter (forward phase shift, 6 dB/octave); interpolation of faulty channels. Baseline correction was conducted in MATLAB 7.14 (MathWorks, Natick, Massachusetts) using the 100 ms
immediately prior to stimulus presentation. Further preprocessing was completed within the MATLAB toolbox Statistical Parametric Mapping 8 (SPM8; http://www.fil.ion.ucl.ac.uk/spm/); trials which reached the threshold of ± 80 µV within the critical peri-stimulus time window of -200 to 1500 ms were identified and rejected, along with any channel in which ≥20% of total trials were artifactual. Finally, data were re-referenced to the average over the scalp electrodes. Further processing was conducted in MATLAB. For each participant, the amplitude was averaged over the nine central electrodes (FC1, FCz, FC2, C1, Cz, C2, CP1, CPz, CP2) in each condition (self- and other-blame) in the 100-300 ms post-stimulus presentation (this time window was selected objectively, being the first peak in the global field power; this is reported in Chapter 2.3.3). Time-frequency decomposition was then conducted for each condition for each participant. Condition-specific power was averaged across all 64 electrodes in the frequency bands theta (4-8 Hz) and alpha (8-14 Hz) in three separate time windows: 100-300 ms, 300-400 ms and 400-700 ms post-stimulus presentation (again selected from global field power; reported in Chapter 2.3.3). These values were extracted for each participant.

3.3.5 Questionnaire measures
Two questionnaire measures were used for correlation with electrophysiological measures: 1) the self-hate subscale of the Interpersonal Guilt Questionnaire (O'Connor et al., 1997), also see Appendix to this chapter; 2) a self-contempt bias score, which was calculated from post-fMRI ratings of the specific feelings experienced during the VMST stimuli (the percentage of trials rated as contempt towards others was subtracted from the percentage of trials rated as self-contempt; previously reported in (Green et al., 2013b)). The self-hate score was missing for one rMDD participant.

3.3.6 fMRI acquisition
T2*-weighted echo-planar images (3 separate runs of 405 volumes, with 5 dummy scans at the start, lasting 13 minutes and 40 seconds each) were acquired on an MRI scanner (3T Achieva, Philips) with an 8-channel head coil. 35-40 x 3 mm slices (dependent on individual head size) with ascending continuous acquisition parallel to the anterior to posterior commissural line. The following parameters were used:
repetition time: 2000 ms; echo time: 20.5 ms; field of view: 220 x 220 x 120 mm; acquisition matrix: 80 x 80 voxels; reconstructed voxel size: 2.29 x 2.29 x 3mm; sensitivity encoding factor 2). This method was previously reported by (Green et al., 2012) and (Lythe et al., in press).

T1-weighted, magnetization-prepared, rapid-acquisition gradient-echo structural images (160 x 0.9 mm axial slices) were also taken. The following parameters were used: repetition time: 8.4 ms; echo time: 3.9 ms; field of view: 240 x 191 x 144 mm; acquisition matrix: 256 x 163 voxels; reconstructed voxel size: 0.94 x 0.94 x 0.9mm; flip angle: 8°. Axial T2-weighted structural images were also acquired for each participant to detect any vascular and inflammatory abnormalities. This method was previously reported by (Lythe et al., in press).

3.3.7 fMRI preprocessing
Preprocessing was completed using SPM8. Functional T2* images were realigned, unwarped and coregistered to the participant's T1 images, and then segmented. Segmentation parameters were used to normalise the images, which were then smoothed with a kernel of 6mm full-width half-maximum.

A BOLD first level model was made for each participant using all trials from the VMST, split into four categories by agency (self or other) and then unpleasantness ratings (high or low). Null events and realignment parameters for all three runs were also included. The temporal and spatial derivatives of the haemodynamic response function were modelled. This method was adapted from one previously reported by (Lythe et al., in press).

3.3.8 fMRI analysis
A composite electrophysiological score (defined later as the “theta power interaction score”) was entered as a covariate of interest in a one-sample t-test model of the self-blame > other-blame BOLD contrast. An inclusive gray matter mask was used. Small volume correction was then used to correct for multiple comparisons over three specific regions of interest (ROIs), all associated with self-blame: BA10, the dorsolateral prefrontal cortex (dLPFC) and the subgenual cingulate and septal region (SCSR). In rMDD, BA10 has shown self-blame-selective decoupling with the anterior temporal lobe (Green et al., 2012), an area associated with conceptual knowledge (Lambon Ralph, 2013); this was thought to represent reduced integration.
of knowledge of social action concepts with knowledge of their future consequences (Green et al., 2012). The dlPFC is associated with protecting against overgeneral forms of self-blame through reduced interdependence of emotional intensity and differentiation between social concepts (Green et al., 2013a). The SCSR is implicated in self-blame, specifically guilt, in both HC (Zahn et al., 2009c) and rMDD (Green et al., 2012) groups. The latter two ROIs were taken from a previous study (Zahn et al., 2009c), and their creation is described fully in its supplement. In short, the ROIs were created by adapting and combining masks from the Automatic Anatomical Labeling atlas (Tzourio-Mazoyer et al., 2002), which is a feature of the WFU PickAtlas MATLAB toolbox (Maldjian et al., 2003). The BA10 mask was also created using the WFU PickAtlas, but has not been reported previously. The cluster average of general linear model (GLM) regression coefficients were extracted from clusters that survived family-wise error (FWE)-correction.

### 3.4 Results

All statistical analyses were conducted using SPSS20 (http://www.spss.com). Data fulfilled the standard assumptions for each statistical test unless otherwise stated. Table 3.2 contains a summary of all variables studied.

**Table 3.2 Behavioural data for HC and rMDD groups** Non-parametric tests were used where data were not normally distributed

<table>
<thead>
<tr>
<th>Variable</th>
<th>HC</th>
<th>rMDD</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of self-blame trials</td>
<td>49.0 (33-68)</td>
<td>49.4 (30-73)</td>
<td>U = 1091, p = 0.915</td>
</tr>
<tr>
<td>Number of other-blame trials</td>
<td>48.5 (31-67)</td>
<td>48.7 (30-74)</td>
<td>U = 1027, p = 0.564</td>
</tr>
<tr>
<td>FAS score</td>
<td>41.1 ± 9.5</td>
<td>42.5 ± 11.8</td>
<td>t = 0.59, p = 0.559</td>
</tr>
<tr>
<td>Trail-making score</td>
<td>24.9 (5.3-78.5)</td>
<td>22.7 (-1.7-64.0)</td>
<td>U = 1062, p = 0.750</td>
</tr>
<tr>
<td>Self-contempt bias</td>
<td>2.2 (-9.1-17.7)</td>
<td>5.9 (-21.0-37.8)</td>
<td>U = 854, p = 0.065</td>
</tr>
<tr>
<td>Self-hate</td>
<td>20.7 (16-46)</td>
<td>30.2 (17-54)</td>
<td>U = 346.5, p &lt; 0.001</td>
</tr>
<tr>
<td>BDI score</td>
<td>0.8 (0-6)</td>
<td>3.6 (0-17)</td>
<td>U = 525, p &lt; 0.001</td>
</tr>
<tr>
<td>Number of past MDEs</td>
<td>-</td>
<td>3.9 (1-53)</td>
<td>-</td>
</tr>
</tbody>
</table>

Abbreviations: BDI, Beck Depression Inventory; HC, healthy control; MDE, major depressive episode, rMDD, remitted major depressive disorder

#### 3.4.1 Amplitude

A condition difference score for the central 9 electrodes, averaged over 100-300 ms post-stimulus, was created for each participant by subtracting the other-blame amplitude from the self-blame amplitude. This was done as differences in neural response in self- and other-blame conditions was the main variable of interest; difference scores can also increase statistical power in the model (Jamieson, 2007).
This score showed no significant difference between the rMDD and HC groups ($t[98] = 0.269$, $p = 0.788$, see Figures 3.2 and 3.3 for representative amplitude timecourses and topoplots). There was also no significant difference when the two prospective rMDD subgroups were factored into the model with the HC group ($H[2] = 3.797$, $p = 0.150$). However, pairwise comparisons showed a significant difference between the Stable Remission and Recurring Episode subgroups ($U = 198$, $p = 0.031$); this result remained significant when excluding outliers ($U = 178$, $p = 0.016$).

There was no significant difference between the HC group and the Stable Remission or Recurring Episode subgroups ($U \leq 429$, $p \geq 0.268$).\textsuperscript{11}

\textbf{Figure 3.2 Cz amplitude over time} The mean amplitude of the most central electrode over the post-stimulus period, split by condition and cross-sectional groups. This is an illustrative figure; statistics were conducted on the central nine electrodes (see main text).

\textsuperscript{11}NB: The condition difference amplitude score was not normally distributed in the Recurring Episode group, hence non-parametric statistics are used when this group was included. A Kruskal-Wallis H test was used to compare HC, Stable Remission and Recurring Episode groups, and a Mann-Whitney U test was used to compare Recurring Episode with either the Stable Remission or HC group.
Figure 3.3 Cz amplitude over time with topoplots. The black line graph in each plot shows the amplitude over time of Cz, the very central electrode, for each respective condition and group. Topoplots represent the average amplitude, 100-300 ms post-stimulus, across the whole scalp; this time period is indicated by the vertical red lines. The central 9 electrodes (FC1, FCz, FC2, C1, Cz, C2, CP1, CPz, CP2) are indicated by the black square on each topoplot; statistics were conducted on amplitudes averaged across these 9 electrodes (see Sections 3.3.4 & 3.4.1).
3.4.2 Time-frequency decomposition

For each frequency band (theta and alpha), a GLM was conducted with three factors: time window (100-300 ms, 300-400 ms and 400-700 ms), condition (self- and other-blame) and group (rMDD and HC). The frequency spectra over time, split by condition and group, can be seen in Figure 3.4.

**Figure 3.4 Frequency spectra over time** The power of each frequency over time, averaged across all 64 electrodes. Plots are split by condition and group. Yellow boxes indicate the time windows (100-300, 300-400, 400-700 ms) extracted across the theta band (4-8 Hz)
3.4.2.1 Theta

A three-factor interaction of time, condition and group was found by entering the condition difference score into a 2 x 2 repeated measures analysis of variance (ANOVA); the factors were group (rMDD and HC) and time window (100-300, 300-400 and 400-700 ms). The group and time window interaction effect was $F[1, 98] = 3.909, p = 0.051$; this result was confirmed in the same direction without outliers ($F[1, 92] = 2.592, p = 0.111$). There was also a main effect of time ($F[1, 98] = 22.619, p < 0.001$), which remained after excluding outliers ($F[1, 92] = 17.183, p < 0.001$). There was no main effect of group ($F[1, 98] = 0.612, p = 0.436$). The three-factor interaction was due to the rMDD group showing a self-blame-selective increase in power, which persisted over time, whereas this decreased in later time windows in the HC group (see Figure 3.5). See Figure 3.6 for the topography of the theta band over time.

![Figure 3.5 Theta power over time](image)

**Figure 3.5 Theta power over time**  A) Mean theta power of self-blame trials over three post-stimulus time bins. B) Mean theta power of other-blame trials over three post-stimulus time bins. Error bars show the standard error of the mean.

The three-factor interaction had an effect size of 0.2 and 40% power (calculated using GPower (Faul et al., 2007)). To achieve 80% power, a total sample size of 248 would have been required.

In order to study where in the temporal domain the three-factor interaction arose, further difference scores were calculated. A condition difference score was created.
for each participant in each time window by subtracting the other-blame power from the self-blame power. Then a combined “condition-time difference score” was created by subtracting the condition difference scores within each pair of time windows (100-300 minus 300-400, 300-400 minus 400-700 and 100-300 minus 400-700). The condition-time difference score between the first and last time window is hereafter referred to as the “theta power interaction score”.

The theta power interaction score was significantly lower in the rMDD than the HC group (/t/98 = 1.977, /p/ = 0.051), but there were no differences between the Stable Remission and Recurring Episode groups (/t/49 = 0.609, /p/ = 0.545); there were no outliers to remove. There were no group differences for the other condition-time scores (/t/98 < 1.702, /p/ > 0.092). The theta power interaction score did not correlate with measures of residual symptoms (MADRS, GAF or Beck Depression Inventory (Beck et al., 1988)) or with number of past major depressive episodes (/p/ ≥ 0.327; see Table 3.3). The theta power interaction score also showed no correlation with the self-contempt bias score (/rho/ = 0.001, /p/ = 0.995), but did correlate negatively with self-hate (/rho/ = -0.250, /p/ = 0.012); this remained significant when excluding outliers (/rho/ = -0.230, /p/ = 0.022). To investigate group effects on the correlation, a GLM was conducted with theta power interaction score as the dependent variable, group as the fixed factor and self-hate as a covariate. The effect of self-hate on theta power weakened when group was factored in; self-hate is known to be elevated in rMDD compared to HCs (Green et al., 2013b). However a trendwise association between self-hate and theta power remained that was independent of group (/F/1,96 = 3.032, /p/ = 0.085). There was no main effect of group on theta power (/F/1,96 = 0.676, /p/ = 0.413).

Table 3.3 Correlations of clinical variables with the theta power interaction score

<table>
<thead>
<tr>
<th>Variable</th>
<th>Spearman’s rho value</th>
<th>/p/ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MADRS</td>
<td>0.058</td>
<td>0.564</td>
</tr>
<tr>
<td>GAF</td>
<td>0.067</td>
<td>0.508</td>
</tr>
<tr>
<td>Beck Depression Inventory</td>
<td>-0.099</td>
<td>0.327</td>
</tr>
<tr>
<td>Past major depressive episodes (rMDD group only)</td>
<td>-0.013</td>
<td>0.920</td>
</tr>
<tr>
<td>Self-contempt bias score</td>
<td>0.001</td>
<td>0.995</td>
</tr>
<tr>
<td>Self-hate</td>
<td>-0.250</td>
<td>0.012</td>
</tr>
<tr>
<td>Self-hate (excluding outliers)</td>
<td>-0.230</td>
<td>0.022</td>
</tr>
</tbody>
</table>
Figure 3.6 Topoplots of theta power over time: Each topoplot shows the theta power intensity over the scalp; split by group, condition and post-stimulus time bin. Direction of power (positive or negative) is relative to pre-stimulus baseline.
### 3.4.2.2 Alpha

The same model was used for the alpha band as was used in the theta band. There was a significant main effect of time ($F[1, 98] = 5.048, p = 0.027$), which remained significant when excluding outliers ($F[1, 94] = 4.270, p = 0.042$). This result was due to both groups showing a self-blame-selective increase in power over time (see Figure 3.7). There was no significant main effect of group ($F[1, 98] = 0.254, p = 0.615$) or interaction between time and group ($F[1, 98] = 0.369, p = 0.545$). See Figure 3.8 for the topography of the alpha band over time.

---

**Figure 3.7 Alpha power over time**  A) Mean alpha power of self-blame trials over three post-stimulus time bins. B) Mean alpha power of other-blame trials over three post-stimulus time bins. Error bars show the standard error of the mean.
Figure 3.8 Topoplots of alpha power over time Each topoplot shows the alpha power intensity over the scalp; split by group, condition and post-stimulus time bin. Direction of power (positive or negative) is relative to pre-stimulus baseline.
3.4.3 fMRI analysis

In the whole-brain analysis using the theta power interaction score as a covariate, there were no surviving voxels using FWE-correction (at \( p < 0.05 \)) at peak-, cluster- or set-level. There were also no surviving voxels after small volume correction in BA10 or the SCSR. Results surviving small volume correction over the dlPFC ROI are shown in Table 3.4 and Figure 3.9.

Table 3.4 Self-blame > other-blame BOLD effects Across all participants using theta power interaction score as a covariate

<table>
<thead>
<tr>
<th>Region</th>
<th>Cluster size</th>
<th>BA</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>t-value</th>
<th>FWE-corrected p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right anterior dlPFC/lateral FPC</td>
<td>209</td>
<td>10</td>
<td>38</td>
<td>52</td>
<td>0</td>
<td>3.89</td>
<td>0.039*</td>
</tr>
</tbody>
</table>

Abbreviations: BA, Brodmann area; dlPFC, dorsolateral prefrontal cortex; FPC, frontopolar cortex; FWE, family-wise error; MNI, Montreal Neurological Institute; ROI, region of interest

*Region survives cluster-level FWE correction over the a priori dlPFC ROI

Figure 3.9 The positive effect of theta power interaction score as a covariate on the BOLD self-blame > other-blame contrast The EEG theta power interaction score was entered as a covariate of interest in a BOLD model of self-blame > other-blame. The model included all participants, irrespective of group. Red circles indicate regions surviving at \( p < 0.05 \), after small volume correction over a dlPFC ROI (see Table 3.4). Coronal, sagittal and axial views shown from co-ordinate \( x = 38, y = 52, z = 0 \) (Montreal Neurological Institute co-ordinates)
3.4.3.1 fMRI regression coefficient analysis

The regression coefficient average extracted from this surviving dIPFC cluster did not differ between the HC and rMDD groups \((t[77] = 0.298, p = 0.766)\), or the Stable Remission and Recurring Episode groups \((t[36] = 0.962, p = 0.342)\). However, this regression coefficient average did correlate positively with the theta power interaction score across all participants \((R = 0.458, p < 0.001)\); this remained when excluding outliers \((R = 0.433, p < 0.001)\). To investigate group effects on the correlation, a GLM was conducted with the dIPFC regression coefficient as the dependent variable, group as the fixed factor, theta power interaction score as a covariate and an interaction term. This GLM showed a main effect of theta power interaction score \((F[1, 75] = 18.118, p < 0.001)\), which remained when excluding outliers \((F[1, 74] = 15.132, p < 0.001)\). There was no effect of group \((F[1, 75] = 0.010, p = 0.921)\) or interaction term \((F[1,75] = 1.233, p = 0.270)\). The correlation found between the dIPFC regression coefficient and theta power interaction score is independent of group.

The regression coefficient average did not correlate with measures of executive function: verbal fluency (as measured by the FAS score (Spreen and Strauss, 1998); \(rho = -0.155, p = 0.173)\); set-shifting (as measured by the trail-making test B-A (Spreen and Strauss, 1998, Saraswat et al., 2006); \(rho = -0.114, p = 0.322)\).

3.5 Discussion

This study investigated self-blame-selective changes in theta and alpha activity in an rMDD compared to an HC group. The main hypothesis was that self-blame-selective group differences would be seen in both frequency bands. We also hypothesised that these differences would also distinguish the Stable Remission and Recurring Episode subgroups.

The main hypothesis was corroborated in the theta band; a three-factor interaction of group, condition and time window was seen. This was due to the rMDD group showing a self-blame-selective increase in power, which reduced less over time, relative to the HC group. The theta power interaction score, representing the condition difference between the first and last time window, showed the greatest group difference. Importantly, this score did not correlate with any measures of residual symptoms, and so is not a state marker of MDD. The score also did not
correlate with number of past major depressive episode, so is unlikely to be a scarring effect.

In order to assist with the clinical interpretation of this finding, we used correlations with measures of maladaptive self-blame. Self-hate has been previously shown to be elevated in an rMDD group relative to an HC group (Green et al., 2013b), and shows negative correlation with the theta power interaction score. The HC group showed a higher theta power interaction score than the rMDD group, so we expected this correlation to be in the negative direction. This means that a larger reduction in increased theta from the first to the last time window is adaptive, as it correlated with lower self-hate. The effect of self-hate on theta power did weaken when group was included as a factor, however a trend-wise association remained that was independent of group.

To investigate sources, the theta power interaction score was entered as a covariate of interest into an fMRI model of self-blame, using fMRI data also derived from the VMST. The score showed significant positive correlation with dIPFC activation, independent of group; as the theta power interaction score also correlated with low self-hate, this suggests that dIPFC activation is adaptive. Interestingly, the right dIPFC has previously been implicated in protection against overgeneral self-blame through coupling with the anterior temporal lobe (Green et al., 2013a); this area is thought to be the hub of conceptual knowledge (Lambon Ralph, 2013). Those with high coupling showed adaptive conceptual-emotional integration during self-blame, meaning reduced interdependence of emotional intensity and overgeneralisation of social concepts, and also lower self-hate (Green et al., 2013a). Our results could link to this functional coupling, given the role of theta in synchronisation of distributed brain areas (O'Neili et al., 2013, Klimesch, 1999, Jones and Wilson, 2005); maladaptive sustained theta may correlate with reduced dIPFC activity through aberrant temporal synchronisation. An alternative explanation of the dIPFC correlation is reappraisal of the stimuli. Reappraisal is a cognitive process in which an individual re-interprets a stimulus in order to reduce or alter their emotional reaction (Gross, 1998, Ochsner and Gross, 2005). Activation of the dorsal PFC is generally associated with reappraisal of negative material (Ochsner and Gross, 2005); more specifically, dIPFC activation was seen during negative self-related stimuli (Lemogne et al., 2009), similar to the self-blame stimuli used in the VMST.
Bilateral lesions of the dLPFC have also been associated with increased depressive symptoms (Koenigs et al., 2008). According to this interpretation, our results show that reduction in dLPFC activation indicates deficient reappraisal of the stimuli; again, this could be linked to aberrant network synchrony through the correlation with sustained theta. However, a lack of correlation with measures of executive function indicates that this interpretation is less likely.

Another ROI, the sgACC, did not show correlation with the theta power interaction score. Given the association of this area with self-blame (Green et al., 2012, Zahn et al., 2009c), and the connection between MDD and ACC theta activity (Arns et al., 2015, Korb et al., 2008, Jaworska et al., 2012), we did not predict this result. Although the sgACC is not always included in studies of theta ACC, Jaworska and colleagues did find elevated theta activity in the sgACC in MDD (Jaworska et al., 2012). Source localisation of the theta power interaction activity would be an interesting next step to see if the robust ACC finding may be linked to self-blame.

The main hypothesis was not corroborated in the alpha band, as no group differences were seen. The interaction of time and condition was significant, due to both groups showing a faster decrease in alpha power over time in self-blame trials compared to other-blame trials. Increased alpha has been associated with attention suppression (Klimesch, 2012); decreasing alpha post-stimulus could represent gradually increased attention. As there were no group differences, this finding has no clinical relevance.

The secondary hypothesis regarding predictive effects was unfortunately not supported in either frequency band. The study was perhaps underpowered to detect predictive effects; given that the theta three-factor interaction had a weak effect size of 0.2 and 40% power, when the sample size was then reduced in the prospective analyses, power would have decreased even further. Replication in a larger sample would be required. However, previous predictive studies of clinical course in MDD have been successful with similar sample sizes (Mulert et al., 2007, Pizzagalli et al., 2001); this indicates that the theta power interaction score is unlikely to have use as a biomarker of vulnerability on an individual level. Similarly, although differences in amplitude were found between the Stable Remission and Recurring Episode subgroups, neither of these differed from the HC group. Therefore we must conclude
that both rMDD subgroups showed responses within the normal range, and so this is also not a useful biomarker of recurrence.

In summary, our findings demonstrated sustained increased theta power during the experience of self-blame relative to other-blame in the rMDD group; this was in contrast to the reduction over time in self-blame-selective increased theta power in the HC group. Self-blame-selective theta also correlated with fMRI activity in the right anterior dIPFC across groups. This region suggests a link to dysfunctional conceptual-emotional integration, possibly through disrupted theta activity altering the temporal binding of the dIPFC with other regions.
Appendix (Chapter 3)

The self-hate subscale of the Interpersonal Guilt Questionnaire.

Each item was rated on the following scale: 1 = very untrue/strongly disagree; 2 = not true/disagree; 3 = sometimes true and sometimes untrue/undecided; 4 = true/agree; 5 = very true/strongly agree.

I do not deserve other people’s respect or admiration.

I deserve to be rejected by people.

I am always expecting to be hurt.

If something bad happens to me I feel I must have deserved it.

If I make a mistake I get very depressed.

If someone blames me for a mishap I assume they are right.

If I fail at something I condemn myself and want to harm myself.

Sometimes I feel I am such a bad person that I don’t deserve to live.

Other people have better lives because they are more deserving than I am.

My parents needed to punish me severely as a child because I did so many bad things.

I always assume I am at fault when something goes wrong.

People would not mistreat me if I did not deserve it.

I feel like an unlovable person.

I feel I am being punished for bad things I did as a child.

Sometimes I feel that I am a selfish and irresponsible person.

I feel there is something inherently bad about me.
References (Chapter 3)


Chapter 4: Reduced EEG source activity in the left anterior dorsolateral frontal cortex in remitted major depression when blaming others

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JG adapted an existing task for use with EEG, with advice from RZ and WE. JG completed all EEG data collection and analyses, with advice from RZ, WE and NT. NT wrote the scripts for psychophysiological interaction analyses. KL conducted all fMRI data collection and analyses. JG, KL, CW and RZ were all involved in participant recruitment and clinical assessments. WE, KL and RZ made helpful comments on the manuscript.
4.1 Abstract

A common symptom of major depressive disorder (MDD) is elevated self-blame (e.g. guilt); this has been shown to persist into remission and is a vulnerability factor to developing further depressive episodes. In recent years, imaging of neural networks related to moral emotions has contributed to the understanding of MDD. However, most studies in this field are conducted using functional magnetic resonance imaging, which has poor temporal resolution. The ‘emotion-feature-event complex model’, a model of moral cognition, states that temporal binding between different brain areas is important for the experience of moral emotions. In order to investigate this, a technique more suited to exploring the temporal dynamics of these interactions, such as electroencephalography (EEG), is required.

Sixty-seven medication-free participants with remitted MDD (rMDD) and 33 healthy controls (HC) with no personal or family history of MDD completed a task designed to evoke feelings related to blaming the self and others, whilst EEG was recorded. A source analysis was conducted to compare activations between groups in self- and other-blaming conditions. Relative to the HC group, the rMDD group showed reduced activation in the left dorsolateral prefrontal cortex (dlPFC) when blaming others. The right homologue showed a trend for the same effect, suggesting the effect is not wholly lateralised. The left dlPFC in particular has previously been associated with anger, but its activation did not correlate with the frequency of other-blame experiences in this study. We suggest that reduced activation may alter the quality of other-blaming feelings, which cannot be assessed with a simple measure like the frequency of experiences. Further work with more detailed ratings is required to confirm this.
4.2 Introduction

Excessive self-blaming feelings, namely worthlessness and inappropriate guilt, are among the recognised symptoms of major depressive disorder (MDD) (First et al., 2002). Guilt and worthlessness are reported cross-culturally in MDD (Sartorius et al., 1980) and MDD patients consistently show elevated levels of guilt relative to healthy controls (HCs) (Berrios et al., 1992, O'Connor et al., 2002, Jarrett and Weissenburger, 1990). In contrast, feelings related to blaming others (e.g. anger) are experienced relatively rarely in MDD without co-morbid disorders (Zahn et al., 2015b); this is termed a self-blaming bias.

Dysfunctional attributions of blame towards the self have also long been associated with vulnerability to developing MDD (Abramson et al., 1978). Excessive self-blame has been shown to predict increased likelihood of a subsequent major depressive episode (MDE) in both pre-school children (Luby and Belden, 2012) and adolescents (Kouros et al., 2015). Self-blaming biases have also been shown to persist in those with remitted MDD (rMDD) (Ghatavi et al., 2002, Green et al., 2013b, Zahn et al., 2015a), who are at high risk of future MDEs (Solomon et al., 2000); this further highlights the role of self-blame as a vulnerability factor. This also emphasises the importance of conducting research with rMDD groups to further understand vulnerability to depression (Bhagwagar and Cowen, 2008).

The advent of neuroimaging techniques has contributed to our understanding of the neuroanatomy of MDD and its specific symptoms. An area of interest in MDD is the subgenual cingulate cortex (sgACC). This area shows altered perfusion and metabolism in MDD (Drevets et al., 1998, Ebert and Ebmeier, 1996), and shows changes after antidepressant treatment (Ressler and Mayberg, 2007). The sgACC is also a successful target for deep brain stimulation in treatment-refractory MDD (Mayberg et al., 2005). Interestingly, functional magnetic resonance imaging (fMRI) studies have shown the sgACC to be selectively active during the experience of guilt (Zahn et al., 2009a, Zahn et al., 2009c). Another area associated with the experience of guilt is the anterior temporal lobe (ATL). In HCs, the ATL is consistently activated during the experience of moral feelings (e.g. guilt, indignation, pride) regardless of valence or agency (Zahn et al., 2007, Zahn et al., 2009c); the level of activation also correlated with increasing conceptual detail of the stimuli (Zahn et al., 2009c). The role of the ATL as a hub of context-independent social conceptual
knowledge (Zahn et al., 2007), i.e. knowledge of the meaning of concepts related to social behaviour, is supported by evidence from semantic dementia. This is a neurodegenerative condition in which there is a selective decline in conceptual knowledge (Hodges et al., 1992). Indeed, semantic task ability correlates positively with the level of ATL atrophy (Mummery et al., 2000).

Dysfunction within a network including the ATL and the sgACC and adjacent septal region (SCSR) has recently been explored using an fMRI task designed to evoke feelings related to blaming the self and others. A psychophysiological interaction (PPI) analysis showed a self-blame-selective decrease in ATL-SCSR functional integration in an rMDD group relative to an HC group (Green et al., 2012). Decreased integration between an area associated with feelings of guilt (sgACC) and an area associated with detailed social conceptual knowledge (ATL) was hypothesised to represent the overgeneralisation of self-blaming feelings (Green et al., 2012) typical of MDD (First et al., 2002). It is thought that in a correctly functioning connection, the ATL enriches the feeling of guilt with social meaning to avoid such overgeneralisation (Moll et al., 2005, Green et al., 2012). More recently, a self-blame-selective hyperconnectivity between the same regions was shown to distinguish rMDD participants who subsequently developed a recurring episode from those who remained in stable remission. The direction of this effect was unexpected, and was attributed to the increased risk of recurrence in the more recent rMDD cohort (i.e. more previous MDEs); the hypoconnectivity found previously could be a marker of resilience against recurrence rather than vulnerability (Lythe et al., in press). Although the direction of the abnormality (i.e. hypoconnectivity or hyperconnectivity) does require clarification, abnormal self-blame-selective ATL-SCSR coupling shows promise as a biomarker for the prediction of depression.

However, this potential biomarker has thus far only been explored using fMRI, which has poor temporal resolution (Luck, 2014). As the functional integration of brain areas is thought to be important for experiencing moral emotions (Moll et al., 2005), a technique better suited to investigating the temporal dynamics of these interactions, is required. Additionally, the cost of fMRI is a potential barrier to its translation to clinical practice (Luck, 2014). Electroencephalography (EEG) (Luck, 2014) has the potential to lessen both these issues. Its temporal resolution is much higher than fMRI (Fabiani et al., 2007). EEG is also cheaper by many orders of
magnitude both to buy and run (Luck, 2014); development of an equivalent biomarker in EEG would be much more cost effective and also more feasible for widespread use given its portability (Gabriel et al., 2015). Although EEG has poorer spatial resolution than fMRI (Luck, 2014), source analysis techniques have allowed localisation of the signal in brain space rather than just the scalp space (Litvak et al., 2011). This allows PPI analyses to be run on EEG data, and allows for the study of functional connectivity within the brain at a much higher temporal resolution than fMRI.

In the present study, we used the same task as previous fMRI studies (Green et al., 2012, Lythe et al., in press) with EEG in medication-free rMDD and HC groups. The rMDD group also completed a longitudinal phase of the study to investigate predictive effects. The sources of EEG activity were localised, and two separate analyses conducted: a simple source activation analysis, and a PPI analysis. Based on two previous fMRI studies using the same task in a similar population ((Lythe et al., in press) and Karen Lythe, personal communication), in the simple activation analysis we predicted a self-blame-selective increase in sgACC activation in the rMDD group relative to the HC group, but no predictive effects. In the PPI analysis, we expected group differences in self-blame-selective ATL-sgACC connectivity, in both the cross-sectional and prospective analyses. Given the similarity of the participant cohort of the present study and our most recent study (Lythe et al., in press), we hypothesised that the direction of effects would be the same. We therefore expected self-blame-selective hyperconnectivity in: 1) the rMDD group relative to the HC group; 2) those who developed a recurring episode relative to both those who remained in stable remission and the HC group. As previously, we did not expect to see any group effects on physiological coupling (i.e. coupling irrespective of psychological condition) (Green et al., 2012).

4.3 Method

4.3.1 Participants
Potential participants responded to advertisements, in both print and online media, for the UK Medical Research Council-funded project “Development of Cognitive and Imaging Biomarkers Predicting Risk of Self-Blaming Bias and Recurrence in Major Depression”. After receiving full information about the study, 707 participants
gave oral consent to an initial screening interview via telephone. Suitable participants gave written informed consent and were assessed by a senior psychiatrist (RZ) and with the Structured Clinical Interview-I for DSM-IV (First et al., 2002). For inclusion in the rMDD group, participants had at least one major depressive episode of two-month duration, had been in remission for at least six months and were free from centrally-active medication (except hormonal contraceptives). They also had no current co-morbid or relevant past axis-I disorders. For the HC group, participants had no personal or first-degree family history of MDD. For full details of inclusion and exclusion criteria and recruitment procedures, see Chapter 2.1, including Table 2.1 which details exclusion reasons up to and including the EEG part of the study. The recruitment procedure is also documented in the Supplemental Materials of previous work (Zahn et al., 2015a). Participants were reimbursed for their time and travel costs. This research study was approved by the South Manchester NHS Research Ethics Committee (reference number: 07/H1003/194).

As part of this larger study, 71 rMDD and 36 HC participants completed a social action judgement task whilst EEG was recorded. Of these, 7 participants were excluded from analyses: n = 1, neurological abnormality on magnetic resonance imaging scan; n = 2, fulfilled criteria for current depression at EEG session; n = 4 insufficient trials for analysis after artifact removal (<30 trials per condition).

67 rMDD and 33 HC participants were included in the final cross-sectional analysis. The two groups did not differ on years of age (rMDD: median 36, range 18-64, HC: median 27, range 20-64, U = 930, p = 0.198), years of education (rMDD: median 17, range 12-22, HC: median 17, range 14-25, U = 900, p = 0.127), or gender (rMDD: 48 females, HC: 22 females, χ² = 0.261, p = 0.610). The Global Assessment of Functioning (GAF) Scale (First et al., 2002) showed that the HC group had higher levels of social and occupational functioning and lower symptom levels (rMDD: median 90, range 70-90, HC: median 90, range 81-90, U = 651.5, p < 0.001).

However, all participants had no more than mild symptoms or functioning problems. All participants also had Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery and Åsberg, 1979) scores below the threshold for depression (<10 points), but the rMDD group showed a trend for higher scores (rMDD: median 0, range 0-6, HC: median 0, range 0-4, U = 919, p = 0.086).
The rMDD participants were also followed up for 14 months after the initial clinical assessment. This created two “prospective” rMDD subgroups: those who remained in “Stable Remission” \((n = 31)\) and those who had a “Recurring Episode” \((n = 20)\). Some participants \((n = 10)\) developed significant symptoms, but did not reach the threshold for a major depressive episode, so are not included in the prospective analysis. These participants had a Psychiatric Status Rating (Keller et al., 1987) of 4, or 3 if treatment was required. Six participants did not complete the follow-up phase of the study, and so are also not included in the prospective analysis. The Stable Remission and Recurring Episode groups did not differ on years of age, years of education, gender, GAF score or MADRS score (see Table 4.1).

### Table 4.1 Demographics of Stable Remission and Recurring Episode groups

<table>
<thead>
<tr>
<th></th>
<th>Stable Remission</th>
<th>Recurring Episode</th>
<th>Statistic</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>39 (20-63)</td>
<td>37 (18-64)</td>
<td>(U = 293.5)</td>
<td>0.750</td>
</tr>
<tr>
<td>Education (years)</td>
<td>17 (14-22)</td>
<td>17 (12-20)</td>
<td>(U = 233.5)</td>
<td>0.134</td>
</tr>
<tr>
<td>Gender</td>
<td>22 F, 9 M</td>
<td>12 F, 8 M</td>
<td>(X^2 = 0.658)</td>
<td>0.417</td>
</tr>
<tr>
<td>MADRS score</td>
<td>0 (0-4)</td>
<td>0 (0-6)</td>
<td>(U = 282.5)</td>
<td>0.538</td>
</tr>
<tr>
<td>GAF score</td>
<td>90 (70-90)</td>
<td>85.5 (70-90)</td>
<td>(U = 249.5)</td>
<td>0.205</td>
</tr>
</tbody>
</table>

Data are shown in the format: median (range). F = female, M = male.

#### 4.3.2 Value-related moral sentiment task

The value-related moral sentiment task (VMST) is a 180-item social action judgement task designed to explore neural correlates of moral emotions associated with blame attribution. Each stimulus is a short sentence describing an action between the participant and their best friend. The action is always counter to accepted social norms, in either negative or negated positive form, e.g. “Joe [the participant] acts stingily towards James [his best friend]”. In half the stimuli \((n = 90)\), the participant is the agent and the best friend is the recipient. In the other half, the roles are reversed but the rest of the sentence remains identical, e.g. “James acts stingily towards Joe”; both conditions are balanced on verbal working memory load, syntax and semantics. Stimuli were taken from previous normative studies (Zahn et al., 2007, Zahn et al., 2009c), and the paradigm was adapted for EEG from a previous fMRI study (Green et al., 2012).

Stimuli were presented in a pseudo-random order over three counterbalanced runs. To account for the higher temporal resolution of EEG (Fabiani et al., 2007), stimuli were presented for a shorter time (2.2 seconds) and in shortened form for faster
reading, e.g. “Joe stingy James” (see Figure 4.1). In the following 2 seconds, participants made a button press response on whether the sentence made them feel “mildly unpleasant” or “very unpleasant”. Finally, participants completed a simple calculation as a distraction, and then a null fixation condition preceded the next stimulus to allow for baseline subtraction.

In a previous study session, participants also made more detailed unpleasantness ratings on each sentence using a 7-point Likert scale. These subjective ratings allowed trials to be categorised for each participant individually. The present study analysed trials related to self-blame and other-blame only; this was assumed to be trials which were rated as highly intensely unpleasant (trials rated as the median or above, or >1 if the median was 1) in the self- and other-agency conditions respectively. Participants also selected the feeling that they most associated with each stimulus from: guilt, contempt/disgust towards oneself, anger/indignation towards oneself, shame, contempt/disgust towards friend, anger/indignation towards friend, no feeling or other feeling.

**Figure 4.1 VMST schematic** An example self-agency trial from the EEG version of the VMST; presentation times are shown below each screen.
4.3.3 EEG acquisition
EEG was recorded at 512 Hz with a 64-electrode ActiveTwo system and Actiview acquisition software (BioSemi, Amsterdam, Netherlands). EEG electrode placement followed the 10-20 International System (Pizzagalli, 2007). In Biosemi systems, the ground electrode is replaced with one active and one passive electrode; they form a feedback loop to drive the common mode voltage of the participant as close as possible to the analog-to-digital converter reference voltage (the amplifier “zero”). Full details can be found at http://www.biosemi.com/faq/cms&drl.htm. Four external electrodes measured the horizontal and vertical electrooculogram; these were placed at the outer canthus of each eye and above and below the right eye.

4.3.4 EEG preprocessing
Brain Electrical Source Analysis 5.2 (BESA GmbH, Gräfelfing, Germany) was used for the following preprocessing steps: removal of artifacts from vertical and horizontal eye movements (threshold ± 100 µV); 1 Hz high-pass filter (forward phase shift, 6 dB/octave); interpolation of faulty channels. Baseline correction was conducted in MATLAB 7.14 (MathWorks, Natick, Massachusetts) using the 100 ms immediately prior to stimulus presentation. Further preprocessing was completed within the MATLAB toolbox Statistical Parametric Mapping 8 (SPM8; http://www.fil.ion.ucl.ac.uk/spm/); trials which reached the threshold of ± 80 µV within the critical peri-stimulus time window of -200 to 1500 ms were identified and rejected, along with any channel in which ≥20% of total trials were artifactual. Finally, data were re-referenced to the average over the scalp electrodes.

4.3.5 Source analysis
(A more detailed explanation of the source analysis methods can be found in Section 2.3.4)

For each participant, an average over trials in each condition (self- and other-blame) was created, termed the condition average. Source reconstruction was then computed on the condition averages in SPM8. A model of the inner skull, outer skull and scalp, along with a cortical mesh of 8196 vertices (corresponding to potential brain sources (Litvak et al., 2011)), was generated from the SPM8 template MRI scan. Co-registration was conducted using five EEG electrode positions as fiducials (Iz, FPz, Cz, T7 and T8). The forward model was calculated using a Boundary Elements
Model. The inverse reconstruction step used a greedy search multiple sparse priors algorithm (Ashburner et al., 2013). A thresholded statistical mask was included as a prior to improve the solution; this was created from data from an associated fMRI study using the VMST in the same participants (a more detailed description of fMRI acquisition and preprocessing can be found in Chapters 3 and 5). The mask was the combination of two blood-oxygen-level dependent contrasts (self-blame > fixation and other-blame > fixation) from 37 HC and 69 rMDD participants. Suprathreshold clusters from the mask are given more weight in the solution, but are only incorporated into the solution if they improve the fit of the model (Litvak et al., 2011). Evoked power between 1 and 50 Hz was localised at 300-400 ms for each condition average (this time window was selected objectively using global field power; this is reported in Chapter 2.3.3). Resulting images were smoothed at 10 mm. Full factorial models with two factors, group and condition, were conducted for: the cross-sectional groups (HC and rMDD) and the prospective groups (HC, Stable Remission and Recurring Episode). F tests to investigate main effects of group, condition and interaction effects were performed.

4.3.6 Psychophysiological interaction analysis

(A more detailed explanation of the PPI analysis methods can be found in Section 2.3.5)

The above source reconstruction was repeated at the single trial level to allow PPI analyses to be completed.

A PPI analysis was conducted to investigate condition-related differences in the functional connectivity of a seed region and other brain regions (Friston et al., 1997). The seed co-ordinate, $x = 58, y = -4, z = -4$ (co-ordinates are given in Montreal Neurological Institute [MNI] space), was selected based on an analysis of sources across all participants and both conditions (self- and other-blame); see Figure 2.5. This co-ordinate was the peak of the cluster which was most centrally located within the anterior superior temporal area, an area known to be involved in processing of social concepts (Zahn et al., 2007, Zahn et al., 2009c). Using MATLAB, the seed signal (the physiological signal irrespective of psychological condition) was extracted from an 8 mm sphere around the seed co-ordinate. This was then multiplied by the psychological condition (i.e. self- or other-blame) to give the effect
of the psychological condition on the physiological signal (the PPI interaction term). This analysis approach has previously been used with VMST fMRI data (Green et al., 2012, Lythe et al., in press). For each participant, a multiple regression model was run using the physiological and psychological variables and the PPI interaction term.

Contrasts representing the difference between self- and other-blame for the PPI interaction term were produced and smoothed at 10 mm; this enabled comparison of functional connectivity between the seed region and other brain regions in the two different conditions. These smoothed contrast images were taken to the group level for statistical analysis: a two-sample t test for the cross-sectional groups (rMDD vs. HC) and a one-way ANOVA for the prospective groups (HC, Stable Remission and Recurring Episode). This identified group differences in connectivity with the seed region in one condition relative to the other. The same analysis was conducted using a contrast representing the difference between self- and other-blame for the physiological variable, to investigate ATL functional connectivity irrespective of psychological condition.

4.3.7 Regions of interest
A priori regions of interest (ROIs) were further investigated in the results of both the simple source analyses and PPI analyses.

Small volume correction was used to investigate a priori ROIs in relevant results; co-ordinates were taken from previous independent studies (Green et al., 2010, Green et al., 2013a), and 5 mm spheres were used around these co-ordinates, as in a previous similar study (Green et al., 2010). To investigate the subgenual cingulate, an area which is implicated in self-blame in MDD (Green et al., 2012), we used x = -4, y = 23, z = -5 (Green et al., 2010). To investigate the anterior dorsolateral prefrontal cortex (dlPFC), we used x = 40, y = 40, z = 16 (and its left hemisphere homologue) (Green et al., 2013a). This area has been implicated in protecting against overgeneral forms of self-blame through reduced interdependence of emotional intensity and overgeneralisation of social concepts (Green et al., 2013a). Significant results were further examined in SPSS (http://www.spss.com); the signal amplitude was averaged over the cluster of interest and extracted using SPM8 toolbox MarsBaR (http://marsbar.sourceforge.net/).
4.4 Results

Table 4.2 contains a summary of all variables studied.

**Table 4.2 Behavioural data for HC and rMDD groups** Non-parametric tests were used where data were not normally distributed

<table>
<thead>
<tr>
<th>Variable</th>
<th>HC</th>
<th>rMDD</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of self-blame trials</td>
<td>49.0 (33-68)</td>
<td>49.4 (30-73)</td>
<td>U = 1091, p = 0.915</td>
</tr>
<tr>
<td>Number of other-blame trials</td>
<td>48.5 (31-67)</td>
<td>48.7 (30-74)</td>
<td>U = 1027, p = 0.564</td>
</tr>
<tr>
<td>FAS score</td>
<td>41.1 ± 9.5</td>
<td>42.5 ± 11.8</td>
<td>t = 0.59, p = 0.559</td>
</tr>
<tr>
<td>Trail-making score</td>
<td>24.9 (5.3-78.5)</td>
<td>22.7 (-1.7-64.0)</td>
<td>U = 1062, p = 0.750</td>
</tr>
<tr>
<td>BDI score</td>
<td>0.8 (0-6)</td>
<td>3.6 (0-17)</td>
<td>U = 525, p &lt; 0.001</td>
</tr>
<tr>
<td>Number of past MDEs</td>
<td>-</td>
<td>3.9 (1-53)</td>
<td>-</td>
</tr>
</tbody>
</table>

Abbreviations: BDI, Beck Depression Inventory; HC, healthy control; MDE, major depressive episode, rMDD, remitted major depressive disorder

4.4.1 Source analysis

4.4.1.1 Cross-sectional groups

The whole brain analysis showed no surviving voxels using family-wise error (FWE)-correction (at p < 0.05) at peak-, cluster- or set-level. The F tests for main effects of group and condition also showed no surviving voxels after small volume correction. Results for the F test of group and condition interaction are shown in Figure 4.2; results after small volume correction for the left anterior dorsolateral prefrontal cortex are shown in Table 4.3. The right homologue of this region did not survive small volume correction (FWE-corrected p = 0.058).

![Figure 4.2 Regions showing an interaction of group and condition](image)

Figure 4.2 Regions showing an interaction of group and condition EEG sources showing an interaction between group (rMDD and HC) and condition (self- and other-blame). Coronal, sagittal and axial views are shown from co-ordinates x = -40, y = 40, z = 16 (MNI co-ordinates). Image is thresholded at p < 0.05 (uncorrected).
Table 4.3 EEG source analysis effects for the cross-sectional groups Results of the F test for interaction for group and condition (see also Figure 4.2)

<table>
<thead>
<tr>
<th>Region</th>
<th>Cluster size</th>
<th>BA</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>F-value</th>
<th>FWE-corrected p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left anterior dorsolateral frontal cortex</td>
<td>390</td>
<td>10</td>
<td>-40</td>
<td>40</td>
<td>20</td>
<td>5.79</td>
<td>0.032*</td>
</tr>
</tbody>
</table>

Abbreviations: BA, Brodmann area; FWE, family-wise error; MNI, Montreal Neurological Institute; ROI, region of interest

*Region surviving peak-level FWE correction over the a priori left dlPFC ROI

In order to investigate the direction of the interaction effect, the signal amplitude was averaged over and extracted from the left dlPFC cluster for analysis in SPSS. The group and condition interaction effect was confirmed ($F[1, 98] = 5.733, p = 0.019$ [not driven by outliers: $F[1, 91] = 2.999, p = 0.087$]), and again no main effect of group ($F[1, 98] = 1.631, p = 0.205$) or condition was found ($F[1,98] = 1.526, p = 0.220$). The interaction effect was due to the rMDD group showing decreased left dlPFC activity during other-blame relative to the HC group; there were no group differences during self-blame (see Figure 4.3).

Figure 4.3 Left dlPFC signal amplitude EEG source signal amplitudes were averaged over the left dlPFC for each group and condition. Error bars show the standard error of the mean.
A difference score of the signal amplitude was created to represent blame bias (self-blame minus other-blame); blame bias is the main variable of interest. This score did not correlate with measures of residual symptoms of depression (MADRS, GAF or Beck Depression Inventory (Beck et al., 1988), \( p \geq 0.150 \)) or with measures of executive function (verbal fluency, as measured by the FAS score (Spreen and Strauss, 1998); set-shifting as measured by the trail-making test B-A (Spreen and Strauss, 1998, Saraswat et al., 2006), \( p \geq 0.149 \)). There was also no correlation with the number of past MDEs (\( \rho = 0.135, p = 0.275 \)). Additionally, there was no correlation with the percentage of trials rated as an other-blaming feeling (i.e. contempt/disgust or anger/indignation towards friend), \( R = -0.057, p = 0.573 \).

4.4.1.2 Prospective groups
In the full factorial model (including HC, Stable Remission and Recurring Episode), no contrasts showed surviving voxels using FWE-correction (at \( p < 0.05 \)) at peak-, cluster- or set-level, over the whole brain or ROIs.

4.4.2 PPI analysis

4.4.2.1 Cross-sectional groups
For two-sample t tests (HC vs. rMDD) of both the PPI interaction term and the physiological variable, no contrasts showed surviving voxels using FWE-correction (at \( p < 0.05 \)) at peak-, cluster- or set-level, over the whole brain or ROIs.

4.4.2.2 Prospective groups
For one-way ANOVAs (HC, Stable Remission and Recurring Episode) of both the PPI interaction term and the physiological variable, no contrasts showed surviving voxels using FWE-correction (at \( p < 0.05 \)) at peak-, cluster- or set-level, over the whole brain or ROIs.

4.5 Discussion
This study investigated EEG source activation patterns and functional connectivity in rMDD and HC groups using a task designed to evoke self- and other-blaming feelings. The rMDD group also completed a longitudinal phase of the study, which was used to group participants into “Stable Remission” and “Recurring Episode” subgroups, to investigate predictive effects. We predicted a self-blame-selective increase in sgACC activation in the rMDD group relative to the HC group. In a PPI
analysis, we expected self-blame-selective ATL-sgACC hyperconnectivity in: 1) the rMDD group relative to the HC group; 2) the Recurring Episode subgroup relative to both the HC group and the Stable Remission subgroup. No group effects on physiological coupling (i.e. coupling irrespective of psychological condition) were expected.

The first hypothesis of increased self-blame-selective sgACC activation was not corroborated. Instead, an other-blame selective decrease in left dIPFC activity was seen in the rMDD group relative to the HC group. Additionally, the right dIPFC showed a strong trend for the same effect; although this did not reach significance at the p < 0.05 FWE-corrected level, it is important to note that the effect is not wholly lateralised.

Activation of the dorsal PFC is generally associated with reappraisal of negative material (Ochsner and Gross, 2005). Reappraisal is a cognitive process in which an individual re-interprets a stimulus in order to reduce or alter their emotional reaction (Gross, 1998, Ochsner and Gross, 2005). Relative to the right dIPFC, the left dIPFC is more strongly associated with executive functioning; those with left dIPFC lesions show greater impairments in executive functioning (Alvarez and Emory, 2006), and this area is activated during tests of executive function, such as the trail-making test (Moll et al., 2002). With this evidence, a cognitive control mechanism might be postulated to explain the results. However the signal amplitude of the other-blaming bias showed no correlation with measures of executive function, so we suggest a different mechanism. Anger within a social context, an other-blaming emotion, has been associated with left prefrontal areas (van Honk et al., 2002, Harmon-Jones and Allen, 1998, Zahn et al., 2009c); specifically, trait anger positively correlates with left frontal cortical activity in response to pictures designed to evoke anger (Harmon-Jones, 2007). Highly intensely unpleasant other-blame sentences from the VMST represent a similar stimulus set, which suggests there was a reduced anger response in the rMDD group. Indeed, relative to an HC group, rMDD participants (from a larger cohort which includes participants from the present study) have been shown to display reduced negative emotions towards others, (Zahn et al., 2015a). However, the dIPFC signal amplitude of the other-blaming bias showed no correlation with the percentage of trials rated as an other-blaming feeling (e.g. anger). This indicates that reduced activation of the dIPFC does not result in a reduction in other-blaming
emotions per se; however changes in network activation between the two groups may give rise to a different quality of the experience, which cannot be assessed with a simple measure like the frequency of other-blame experiences.

Right dIPFC lesions have been more strongly associated with disturbances in moral behaviour (Moll et al., 2005), with such patients often displaying problems with social conduct (Miller et al., 1993, Eslinger and Biddle, 2000). Within a healthy population, a voxel-based morphometry study showed that right dIPFC volume negatively correlated with guilt responses in the sgACC (Zahn et al., 2014). This indicates that an rMDD group, shown to have elevated guilt responses in this area (Karen Lythe, personal communication), may have reduced right dIPFC volumes. It is difficult to explain other-blame-selective differences in right dIPFC activation through reduced volume, as this area is also important in self-blame (Green et al., 2013a). A possible explanation involves the role of the dIPFC in representations of non-routine event sequences and consequences; disruption in understanding consequences of actions can explain the social misconduct seen after lesions of this area (Moll et al., 2005). It is possible that this type of event sequence are imagined more in response to the other-blame stimuli, and that the rMDD group therefore showed reduced right dIPFC activation due to reduced cortical volume. A previous study showed no difference between an HC and an rMDD group on the number of consequences imagined in response to either guilt- or indignation-evoking VMST stimuli (Green et al., 2012), however they did not probe the specific nature of these consequences. This result should be interpreted with caution, however, as we did not conduct a volumetric study on the current cohort.

Unfortunately, neither of the PPI hypotheses were corroborated, as group differences were not found in either the cross-sectional or the prospective data. One possible reason for this is the selection of a specific time window (300-400 ms post-stimulus presentation) chosen to be relevant to semantic processing (see Chapter 2.3.3). Previous results from similar studies finding group differences in ATL-SCSR coupling (Green et al., 2012, Lythe et al., in press) were conducted using fMRI, which has comparatively poor temporal resolution (Luck, 2014); it is therefore unknown which time points are most relevant to their results. An analysis of connectivity over different time points may have detected comparable effects, and indeed provided additional temporal information with which to interpret previous
fMRI effects. The time window selection could also explain why the activation results were different to what was hypothesised.

Another contributing factor could be inaccurate source localisation of the EEG signal. Using individual head models is optimal (Henson et al., 2009) but unfortunately, the field of view of the individual structural MRI scans were not suitable for creating a head model, so the same template was used across all participants. Despite this, accurate co-registration of electrodes with this template was still expected to produce a reasonable model (Litvak et al., 2011), and appropriate source priors were included to improve estimation of the solution (Henson et al., 2010). However, a key ROI in these analyses was the sgACC, which is a deep source. Inevitably, sources nearer to the cortical surface contribute more to the EEG signal than deeper sources (Wager et al., 2007), so activity from this area may have been difficult to reliably detect. Additionally, compared to a simple activation analysis where each source is considered individually, the PPI analysis introduces additional variance, as it explores the correlation between two sources; this accumulation of variance may have made group differences difficult to detect. The PPI analysis also required source analysis on a single-trial level, which is inevitably more unreliable than the condition average.

No group differences were seen in the physiological variable from the PPI analysis. As we hypothesised that it is the psychological not the physiological variable that is relevant, this was expected. However, given the lack of group differences in the main PPI analysis, it is difficult to say whether physiological coupling irrespective of psychological condition is indeed less relevant, or if it was simply not detected due to reasons discussed previously.

In summary, our findings demonstrated decreased activation of the left dIPFC during other-blame in the rMDD group relative to the HC group, with a trend for the same effect in the right homologue. No group differences were observed during self-blame. The left dIPFC in particular has previously been associated with anger, but its activation did not correlate with the frequency of other-blame experiences in this study. We suggest that reduced activation may alter the quality of other-blaming feelings, which cannot be assessed with a simple measure like the frequency of experiences. Further work with more detailed ratings is required to confirm this.
References (Chapter 4)


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Chapter 5: Time-locked EEG source signal does not correlate with fMRI BOLD signal during self-blame

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JG adapted an existing task for use with EEG, with advice from RZ and WE. JG completed all EEG data collection and analyses, with advice from RZ and WE. KL conducted all fMRI data collection and analyses. JG, KL, CW and RZ were all involved in participant recruitment and clinical assessments. RZ, KL and WE made helpful comments on the manuscript.
5.1 Abstract

Electroencephalography (EEG) and functional magnetic resonance imaging (fMRI) are complimentary imaging techniques which, when combined, allow temporal and anatomical mapping of cognitive functions. The current study tested the level of correlation of these two modalities in the source space across a clinical and control group during a task designed to evoke self-blame-related feelings. Fifty-nine medication-free participants with remitted major depressive disorder (rMDD) and 31 healthy controls with no personal or family history of MDD completed this task whilst non-simultaneous EEG and fMRI were recorded. Localisation of the EEG signal was conducted in a time window related to semantic processing (300-400 ms post-stimulus onset) to capture emotional judgements related to the meaning of the stimuli. Source priors from the fMRI data were incorporated to improve the model fit. The EEG signal was extracted from two clusters of interest, the right superior temporal region and the ventromedial frontal region. These signals were used as covariates of interest in standard blood-oxygenation-level dependent fMRI models of self-blame to explore positive cross-modality correlation. There were no surviving voxels using family-wise error-correction (at p <0.05) at peak-, cluster- or set-level, before or after small volume correction over regions of interest. Potential explanations for this lack of correlation are discussed. This analysis suggests EEG is not a suitable substitute for fMRI in the spatial localisation of individual differences in self-blame-related neural activity in future studies. However, correlation with the fMRI signal at different time-points within the EEG epoch was not considered here, which could be the basis of future work.
5.2 Introduction

Non-invasive imaging methods, such as electroencephalography (EEG) and functional magnetic resonance imaging (fMRI), can provide us with great insight into the cognitive functions of the brain and how they differ in neuropsychiatric conditions (Zahn, 2009). Standard analyses of these techniques (e.g. event-related potentials [ERPs] and blood-oxygen-level dependent [BOLD]), have opposing limitations of spatial and temporal resolution respectively (Luck, 2014). In the present study investigating neural correlates of self-blaming biases in depression vulnerability, data from both EEG and fMRI was collected in order to benefit from the advantages of both techniques. However, this is not a practical long-term strategy for either large research studies or widespread clinical use; in this sense, EEG has many benefits over fMRI, including: increased affordability to buy and run (Luck, 2014), fewer hardware requirements (Pizzagalli, 2007, Wager et al., 2007), portability (Gabriel et al., 2015) and fewer associated hazards and contraindications (Wager et al., 2007). It was therefore of interest to investigate whether the two modalities showed shared neural correlates of self-blame, to indicate whether EEG alone could be sufficient in future similar studies.

Improvements in source localisation techniques are also increasing the spatial accuracy of EEG. Localising the neural generators of signals detected on the scalp is a mathematically ill-posed problem, as each has infinite source solutions; this is largely because the head acts as a volume conductor (Pizzagalli, 2007). Increasingly realistic models of the different conductive properties of head tissues (Pizzagalli, 2007) are improving the accuracy of source solutions. Additionally, prior expectations based on previously observed data, e.g. activation patterns from fMRI studies, can be included to improve the model (Henson et al., 2010); to avoid biasing the solution, such priors are only incorporated if they improve the model fit (Litvak et al., 2011, Henson et al., 2010).

Human studies have previously shown correlation between EEG in the source space and BOLD signals, even when recorded separately (Vitacco et al., 2002, Whittingstall et al., 2007). However, it has also been shown that the ERP-BOLD relationship changes throughout a trial, suggesting the correlation is specific to a certain time window, which is dependent on the task (Yesilyurt et al., 2010). The context-dependent nature of correlation between fMRI and EEG signals (Yesilyurt et
al., 2010), emphasises the importance of validating correlation in specific tasks; to
our knowledge, cross-modality correlations of the experience of self-blame have not
been studied before. Previous findings of correlation at the group level are also not
consistently found at an individual level, with one study only finding the effect in
half the participants (Vitacco et al., 2002). In the current study, it was important to
validate any correlation across participants with remitted major depressive disorder
(rMDD) and healthy controls (HC); these populations are frequently compared when
studying the role self-blaming bias in depression vulnerability (Green et al., 2012,
Green et al., 2013a).

Two brain regions are known to be consistently activated during the experience of
self-blame and so are of specific interest here. The anterior temporal lobe (ATL) is
involved in processing conceptual knowledge (Lambon Ralph, 2013), particularly
knowledge for social concepts (Zahn et al., 2007, Zahn et al., 2009c). The subgenual
cingulate (sgACC), is implicated in self-blame in both HC (Zahn et al., 2009c) and
rMDD (Green et al., 2012) groups.

The aim of this study was to investigate the correlation of a self-blame-related signal
in two separate imaging sessions using different modalities: EEG projected into the
source space and standard BOLD fMRI. The specific hypothesis was that the
modalities would show correlation in two a priori regions of interest (ROIs) related
to the ATL and sgACC.

5.3 Method

5.3.1 Participants
Potential participants responded to advertisements, in both print and online media,
for the UK Medical Research Council-funded project “Development of Cognitive
and Imaging Biomarkers Predicting Risk of Self-Blaming Bias and Recurrence in
Major Depression”. After receiving full information about the study, 707 participants
gave oral consent to an initial screening interview via telephone. Suitable
participants gave written informed consent and were assessed by a senior psychiatrist
(RZ) and with the Structured Clinical Interview-I for DSM-IV (First et al., 2002).
For inclusion in the rMDD group, participants had at least one major depressive
episode of two-month duration, had been in remission for at least six months and
were free from centrally-active medication (except hormonal contraceptives). They
also had no current co-morbid or relevant past axis-I disorders. For the HC group, participants had no personal or first-degree family history of MDD. For full details of inclusion and exclusion criteria and recruitment procedures, see Chapter 2.1, including Table 2.1 which details exclusion reasons up to and including the EEG part of the study. The recruitment procedure is also documented in the Supplemental Materials of previous work (Zahn et al., 2015a). Participants were reimbursed for their time and travel costs. This research study was approved by the South Manchester NHS Research Ethics Committee (reference number: 07/H1003/194).

As part of this larger study, 71 rMDD and 36 HC participants completed a social action judgement task during separate fMRI and EEG sessions. Of these, 17 participants were excluded from this analysis: \( n = 1 \), neurological abnormality on MRI scan; \( n = 4 \), incomplete fMRI data; \( n = 6 \), excessive head movement on fMRI; \( n = 2 \), fulfilled criteria for current depression at EEG session; \( n = 4 \) insufficient EEG trials for analysis after artifact removal (<30 trials per condition).

59 rMDD and 31 HC participants were included in the final analysis. The two groups did not differ on years of age (rMDD: median 35, range 18-63, HC: median 27, range 20-64, \( U = 773.5, p = 0.231 \)), years of education (rMDD: median 17, range 12-22, HC: median 17, range 14-25, \( U = 703, p = 0.069 \)), or gender (rMDD: 41 females, HC: 21 females, \( \chi^2 = 0.029, p = 0.865 \)). The Global Assessment of Functioning Scale (First et al., 2002) showed that the HC group had higher levels of social and occupational functioning and lower symptom levels (rMDD: median 90, range 70-90, HC: median 90, range 81-90, \( U = 549, p < 0.00 \)). However, all participants had no more than mild symptoms or functioning problems. All participants also had Montgomery-Åsberg Depression Rating Scale (Montgomery and Åsberg, 1979) scores below the threshold for depression (<10 points), and scores did not differ between groups (rMDD: median 0, range 0-6, HC: median 0, range 0-4, \( U = 773.5, p = 0.133 \)).

EEG and fMRI sessions were scheduled as close together as possible, but inevitably the time between sessions varied due to availability of participants and imaging facilities. For the rMDD group, the interval limit was ~3 months; this minimised the likelihood of mood- and energy-related changes, whilst allowing some flexibility to minimise participant dropout. No such limit was imposed upon the HC group, who
were assumed to have more stable mood and energy levels given their lack of past psychiatric symptoms. Overall, there was no difference between the groups in the number of days between sessions (rMDD: median 24, range 1-95, HC: median 13, range 1-351, \( U = 812.5, p = 0.386 \)). Participants were briefly assessed for changes in mood, energy and medication at both imaging sessions; any reports which raised concern were clarified during a subsequent follow-up session as part of the larger longitudinal study. If clinically relevant changes had occurred, the participant was excluded from this analysis.

All participants, regardless of group, were included in the same models to ensure that any correlation was present across both groups, and also to increase power in the analysis.

### 5.3.2 Value-related moral sentiment task

The value-related moral sentiment task (VMST) is a 180-item social action judgement task designed to explore neural correlates of moral emotions associated with blame attribution. Each stimulus is a short sentence describing an action between the participant and their best friend. The action is always counter to accepted social norms, in either negative or negated positive form, e.g. “Jeremy [the participant] acts stingily towards Mark [his best friend]”. In half the stimuli \( (n = 90) \), the participant is the agent and the best friend is the recipient. In the other half, the roles are reversed but the rest of the sentence remains identical, e.g. “Mark acts stingily towards Jeremy”; both conditions are balanced on verbal working memory load, syntax and semantics. Stimuli were taken from previous normative studies (Zahn et al., 2007, Zahn et al., 2009c).

Both the fMRI and the EEG sessions used the same stimuli in a pseudo-random order over three counterbalanced runs, but stimulus presentation was adapted for each modality (see also Chapter 2.2). In fMRI, stimuli were presented for up to 5 seconds, during which participants made a button press response on whether the sentence made them feel “mildly unpleasant” or “very unpleasant”; following their response, a fixation cross was presented for any remaining time. A jittered inter-trial interval of mean duration 4 seconds (range: 2-6 seconds) followed. A null fixation condition \( (n = 90 \) trials) was mixed in amongst the stimulus trials. In EEG, stimuli were presented for 2.2 seconds, as EEG has a higher temporal resolution (Luck,
To allow stimuli to be read in this time, the sentences were presented in a shortened form (e.g., “Jeremy stingy Mark”). Stimuli were followed by a designated response window (2 seconds) to avoid motor artifacts during stimulus presentation. A simple calculation was added after each stimulus as a distraction, given the shortened inter-trial interval. The null fixation condition was added before each stimulus to allow for baseline subtraction, as is standard in EEG analysis.

After the fMRI session, participants rated each sentence for unpleasantness on a 7-point Likert scale. Such subjective ratings allowed trials from both imaging modalities to be categorised for each participant individually. This study analysed trials related to self-blame only; this was assumed to be trials where the participant was the agent, and which were rated as highly intensely unpleasant (trials rated as the median or above, or >1 if the median was 1).

5.3.3 fMRI acquisition
T2*-weighted echo-planar images (3 separate runs of 405 volumes, with 5 dummy scans at the start, lasting 13 minutes and 40 seconds each) were acquired on an MRI scanner (3T Achieva, Philips) with an 8-channel head coil. 35-40 x 3 mm slices (dependent on individual head size) with ascending continuous acquisition parallel to the anterior to posterior commissural line. The following parameters were used: repetition time: 2000 ms; echo time: 20.5 ms; field of view: 220 x 220 x 120 mm; acquisition matrix: 80 x 80 voxels; reconstructed voxel size: 2.29 x 2.29 x 3 mm; sensitivity encoding factor 2). This method was previously reported by (Green et al., 2012) and (Lythe et al., in press).

T1-weighted, magnetization-prepared, rapid-acquisition gradient-echo structural images (160 x 0.9 mm axial slices) were also taken. The following parameters were used: repetition time: 8.4 ms; echo time: 3.9 ms; field of view: 240 x 191 x 144 mm; acquisition matrix: 256 x 163 voxels; reconstructed voxel size: 0.94 x 0.94 x 0.9 mm; flip angle: 8°. Axial T2-weighted structural images were also acquired for each participant to detect any vascular and inflammatory abnormalities. This method was previously reported by (Lythe et al., in press).

5.3.4 fMRI preprocessing and initial analysis
Preprocessing was completed within the MATLAB (MathWorks, Natick, Massachusetts) toolbox Statistical Parametric Mapping 8 (SPM8;
Functional T2* images were realigned, unwarped and coregistered to the participant's T1 images, and then segmented. Segmentation parameters were used to normalise the images, which were then smoothed with a kernel of 6mm full-width half-maximum.

A BOLD first level model was made for each participant using all trials from the VMST, split into four categories by agency (self or other) and then unpleasantness ratings (high or low). Null events and realignment parameters for all three runs were also included. The temporal and spatial derivatives of the haemodynamic response function were modelled. This method was adapted from one previously reported by (Lythe et al., in press).

5.3.5 EEG acquisition

EEG was recorded at 512 Hz with a 64-electrode ActiveTwo system and Actiview acquisition software (BioSemi, Amsterdam, Netherlands). EEG electrode placement followed the 10-20 International System (Pizzagalli, 2007). In Biosemi systems, the ground electrode is replaced with one active and one passive electrode; they form a feedback loop to drive the common mode voltage of the participant as close as possible to the analog-to-digital converter reference voltage (the amplifier “zero”). Full details can be found at http://www.biosemi.com/faq/cms&drl.htm. Four external electrodes measured the horizontal and vertical electrooculogram; these were placed at the outer canthus of each eye and above and below the right eye.

5.3.6 EEG preprocessing and initial analysis

Brain Electrical Source Analysis 5.2 (BESA GmbH, Gräfelfing, Germany) was used for the following preprocessing steps: removal of artifacts from vertical and horizontal eye movements (threshold ± 100 µV); 1 Hz high-pass filter (forward phase shift, 6 dB/octave); interpolation of faulty channels. Baseline correction was conducted in MATLAB 7.14 using the 100 ms immediately prior to stimulus presentation. In SPM8, trials which reached the threshold of ± 80 µV within the critical peri-stimulus time window of -200 to 1500 ms were identified and rejected, along with any channel in which ≥20% of total trials were artifactual. Finally, data were re-referenced to the average over the scalp electrodes.

(A more detailed explanation of the source analysis methods can be found in Section 2.3.4)
Source reconstruction for all participants was computed at the single trial level in SPM8. A model of the inner skull, outer skull and scalp, along with a cortical mesh of 8196 vertices, was generated from the SPM8 template MRI scan. Co-registration was conducted using five EEG electrode positions as fiducials (Iz, FPz, Cz, T7 and T8). The inverse reconstruction step used a greedy search multiple sparse priors algorithm (Ashburner et al., 2013). A thresholded statistical mask was included as a prior to improve the solution; this was created from the BOLD data of 37 HC and 69 rMDD participants using the combination of two contrasts (self-blame > fixation and other-blame [highly intensely unpleasant other-agency trials] > fixation). Suprathreshold clusters from the mask are given more weight in the solution, but are only incorporated into the solution if they improve the fit of the model (Litvak et al., 2011). Evoked power between 1 and 50 Hz was localised at 300-400 ms for each self-blame trial (this time window was selected objectively using global field power; this is reported in Chapter 2.3.3).

Single trial source images were entered into a one-sample t-test model to create contrast images for each participant, which were then entered into a group-level one-sample t-test model. Two sets of co-ordinates of interest (in Montreal Neurological Institute [MNI] space) for cluster selection were taken from previous independent studies: x = 58, y = 0, z = -12 (Green et al., 2012) for the ATL and x = -4, y = 23, z = -5 (Green et al., 2010) for the sgACC. The averaged general linear model regression coefficients were extracted from clusters containing these co-ordinates using SPM8 toolbox MarsBaR (http://marsbar.sourceforge.net/). Both clusters covered large regions: the ATL cluster extended over the superior temporal region (Figure 5.1) and the sgACC cluster (Figure 5.2) covered a large ventromedial frontal area. These clusters will subsequently be referred to by these regional terms.
Figure 5.1 Axial, coronal and sagittal views of the right superior temporal cluster This cluster was selected as it contains the a priori co-ordinates of interest $x = 58$, $y = 0$, $z = -12$ (MNI co-ordinates); the image is also shown from these co-ordinates. The cluster was extracted from a group-level one-sample model of self-blame. All participants, irrespective of group, were included in this model.

Figure 5.2 Axial, coronal and sagittal views of the ventromedial frontal cluster This cluster was selected as it contains the a priori co-ordinates of interest $x = -4$, $y = 23$, $z = -5$ (MNI co-ordinates); the image is also shown from these co-ordinates. The cluster was extracted from a group-level one-sample model of self-blame. All participants, irrespective of group, were included in this model.

5.3.7 EEG-fMRI correlation analysis
The regression coefficients from each EEG cluster extraction were entered as a covariate of interest in a one-sample t-test model of the self-blame > fixation BOLD contrast (a separate BOLD model for each cluster). This was to explore positive
cross-modality correlation. Small volume correction was then used to correct for multiple comparisons over specific regions (ventromedial prefrontal cortex and right superior temporal cortex). These ROIs were taken from a previous study (Zahn et al., 2009c), and their creation is described fully in its supplement. In short, the ROIs were created by adapting and combining masks from the Automatic Anatomical Labeling atlas (Tzourio-Mazoyer et al., 2002), which is a feature of the WFU PickAtlas MATLAB toolbox (Maldjian et al., 2003).

5.4 Results
There were no surviving voxels using family-wise error-correction (at \( p < 0.05 \)) at peak-, cluster- or set-level, over the whole brain or ROIs.

In SPSS20 (http://www.spss.com), the EEG and fMRI regression coefficients were standardised to allow comparison of inter-individual variance across modalities for each cluster (see Figure 5.3).
**Figure 5.3 Comparison of cross-modality variance** Standardised EEG and fMRI regression coefficients for both clusters of interest: a) right superior temporal region; b) ventromedial frontal region. Regression coefficients were extracted from both clusters in both modalities: EEG (group-level one-sample EEG source model of self-blame) and fMRI (group-level BOLD model of self-blame > fixation). Median and inter-quartile range is shown by the boxes, and ranges by the whiskers.
5.5 Discussion

This study investigated the correlation of a self-blame-related signal in two imaging modalities (EEG projected into the source space and standard BOLD fMRI) using the same task in separate sessions. The hypothesis was that the two modalities would show correlation in two a priori ROIs covering superior temporal and ventromedial frontal regions. Our results did not confirm this hypothesis, as no correlation was seen between the two modalities in either ROI. There are multiple reasons why this could be the case.

Of course, the first is that there are substantial differences in the measures that each modality takes. EEG is a direct measure of neural activity, being the sum of post-synaptic potentials of large patches of synchronous neurones (Pizzagalli, 2007, Fabiani et al., 2007). Conversely, fMRI indirectly measures neural activity via associated changes in local haemodynamic activity (Logothetis, 2003). Also, the EEG signal is dominated by pyramidal cells, which lie perpendicular to the surface (Luck, 2014); other cell types that are not arranged in this open field configuration may not contribute at all (Yesilyurt et al., 2010). Pyramidal cell distribution varies considerably, particularly in the ventromedial frontal area (Öngür et al., 2003); relative contribution to EEG and fMRI signal may therefore vary throughout this region. Sources nearer the cortical surface inevitably contribute more to the EEG signal than deep sources (Wager et al., 2007); the ventromedial frontal cluster covered deep sources, particularly the sgACC, so activity from these areas could have been attenuated in EEG relative to fMRI.

There is also the issue of temporal resolution. EEG has a much higher temporal resolution (Fabiani et al., 2007), and in this study was sampled at 512 Hz, meaning a sample was taken approximately every 2 ms. In contrast, the repetition time in the fMRI part of the study was 2000 ms. Additionally, only the 300-400 ms post-stimulus time window from the EEG was used; it is possible that other time windows would have shown correlation with BOLD, as it has previously been shown that the correlation relationship changes throughout the post-stimulus epoch (Yesilyurt et al., 2010). However, the purpose of this study was to identify any correlation using the EEG time window of interest from the source analysis (see Chapter 4), so other time windows were not considered here. A similar time window (350-450 ms) has shown correlation between the ERP amplitude and the BOLD response in the superior
temporal gyrus (Matsumoto et al., 2005) during a visual word semantic priming task. Although not using a source analysis, this demonstrates that correlation is detectable using similar parameters.

Another possibility is inaccurate source localisation of the EEG signal. Individual head models are optimal (Henson et al., 2009) but unfortunately, the field of view of the individual structural MRI scans were not suitable for building a head model, so the same template was used for each participant. Despite this, accurate co-registration of electrodes with this template was still expected to produce a reasonable model (Litvak et al., 2011), and appropriate source priors were included to improve estimation of the solution (Henson et al., 2010).

Time between imaging sessions could also have been a factor. Correlation between EEG sources and the BOLD response in healthy participants has been shown with non-simultaneous data collection ≤1 week apart (Whittingstall et al., 2007). However some sessions were conducted months apart in the current study. Even though care was taken to ensure there were no clinically relevant mood or energy changes, it is possible that more subtle fluctuations may have occurred between sessions, particularly in a clinical population. It has also been implied that complex visual stimuli such as those used in the current study may benefit from simultaneous acquisition of fMRI and EEG (Yesilyurt et al., 2010). However, non-simultaneous acquisition has been used with visual word stimuli to successfully correlate the N400 ERP and the BOLD response (Matsumoto et al., 2005), so this was not expected to be an issue.

Although the basic stimuli were the same for both modalities, there were differences in presentation style. The semantic processing required to process a full sentence compared to sentence fragments may be different; altered neural responses have been observed after changes in syntactic structure (Newman et al., 2001), although these syntactic changes were more significant than in the current study. As the sentences were more fragmented in the EEG presentation, it made practical sense for all participants to complete the fMRI study first. It is possible that this lack of counterbalancing may have altered responses in the EEG study due to prior familiarity with the task stimuli (Nemeth, 2004). However, given each stimulus was presented only once during each imaging session, this is unlikely.
Finally, it is possible that the two signals did correlate, but there was insufficient inter-individual variance to statistically detect an effect (Reuter-Lorenz and Cappell, 2008). However, this explanation is unlikely; for each cluster, variance was found to be similar in both modalities, and ranged over approximately ±2 standard deviations from the mean (see Figure 5.3).

In summary, the findings demonstrated a lack of correlation between fMRI BOLD and EEG source signals during the self-blame condition of the VMST. It is not possible to say with certainty why this was the case, but it is likely due to a combination of factors as discussed above, including selection of time window, source modelling and task changes. This study does not indicate that EEG is a currently viable replacement method for fMRI in studying the sources associated with self-blame, but nevertheless is useful as a complementary method to provide information about timing that is not possible to achieve with fMRI alone. However, there is the possibility of correlation in other EEG time windows, which warrants further exploration.
References (Chapter 5)


Chapter 6: Reduced positive associative memory biases in remitted major depression with early life stress

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JG designed the associative memory for social actions task with input from RZ and AM. JG completed all data collection and analyses, with advice from RZ. JG, KL, CW and RZ were all involved in participant recruitment and clinical assessments. JG and CW independently categorised early life events. AM, KL and RZ made helpful comments on the manuscript. Wael El-Deredy also made helpful comments in his role as PhD supervisor.
6.1 Abstract

Major depressive disorder (MDD) and early life stress (ELS) have long been associated with autobiographical memory overgeneralisation. However, the effect of these two factors on valence- and self-blame-related biases within memory overgeneralisation is still not fully understood. We developed a novel task to investigate the effects of MDD and ELS on such biases in associative memory for detailed social actions. Fifty-three medication-free remitted MDD participants (25 with ELS, 28 without) and 30 healthy control participants with no personal or family history of MDD (24 without ELS) completed this task. No within-group self-blame-related biases, nor any between-group differences in self-blame-related memory retrieval, were found. However, the two groups with no history of ELS showed a bias towards retrieving the contextual detail of the positive stimuli compared to the negative. The remitted MDD group with experience of ELS showed no such bias, and differed significantly from the HC group with no ELS. This indicates that ELS impacts upon valence-related memory biases, although interaction with a history of MDD cannot be discounted; the negative association of the positive bias score with the number of past major depressive episodes (MDEs) may indicate that it is the cumulative trauma of MDEs, combined with ELS, that leads to the selective loss of positive memory. This is an important finding, especially in a remitted MDD population, as a loss of memory specificity only for positive memories could be a vulnerability factor. Further investigation is required to fully understand the interaction of ELS and psychiatric history on memory biases through similar studies in other psychiatric groups and healthy populations.
6.2 Introduction

Overgeneralisation of autobiographical memories (OGM) is when memories lose their temporal and situational context. For example, “I failed one maths exam in high school” might become “I was bad at maths throughout school”. OGM is a known characteristic of those with both current (Liu et al., 2013) and remitted major depressive disorder (rMDD) (Spinhoven et al., 2006). Such individuals retrieve fewer specific memories (Williams and Scott, 1988, Spinhoven et al., 2006, Nandrino et al., 2002) and are generally slower in their retrieval (Liu et al., 2013) when compared to healthy controls (HC) without a history of MDD.

It has been suggested that OGM may predispose individuals to development (van Minnen et al., 2005) and maintenance (Brittlebank et al., 1993, Sumner et al., 2010) of MDD. Even never-depressed participants with a first-degree family history of MDD, who are at high risk of developing MDD, demonstrated increased OGM compared to those with no family history (Young et al., 2013); this suggests it is a vulnerability factor.

Although primarily associated with MDD and depressed mood (van Vreeswijk and de Wilde, 2004), OGM is also seen in post-traumatic stress disorder (PTSD) (Moore and Zoellner, 2007). Stressors, particularly early life stress (ELS), have also been associated with OGM (Crane et al., 2014, Hitchcock et al., 2014, Burnside et al., 2004). An influential theory is that an overgeneral memory style is initially helpful in protecting against retrieving specific traumatic aspects of the memory, thereby reducing negative affect. However, when this retrieval style is learned in childhood, it may be retained into adulthood and generalised to all memories (Williams, 1996). Such “functional avoidance” is one of a triad of factors which Williams proposes is involved in OGM (Williams, 2006). ELS is known to predispose to MDD (Chapman et al., 2004), and OGM development could be a factor in this. However, some studies report no consistent link between ELS and OGM (Wessel et al., 2001, Peeters et al., 2002) and an evaluative review suggested that experiencing depressive or post-traumatic reactions to stressors is linked to OGM, rather than stressful events or a history of ELS alone (Moore and Zoellner, 2007). Of course, ELS predisposes to hyper-responsiveness to stressful events later in life (Maniam et al., 2014), so ELS is still important here. There is currently insufficient evidence to untangle the interactions between ELS, OGM and vulnerability to MDD. It is important to
establish the role of OGM in vulnerability, as it can be reduced through targeted therapy (Williams et al., 2000).

A valence bias in OGM has also been demonstrated in MDD. Early research in this field showed that the responses of currently depressed participants to positive cues are less specific when compared to both negative cues and HC groups (Williams and Scott, 1988); positive responses are also slower compared to neutral (Gupta and Kar, 2012) or negative responses (Kaviani et al., 2005). This valence bias has been shown to persist in remission (Park et al., 2002, Gupta and Kar, 2012). This bias could conceivably precipitate or prolong a depressed state through reduced access to specific positive memories compared to negative ones. This research fits in with the general negative emotionality model of MDD (Watson et al., 1988), which states that reduced positive affect is specific to MDD, and increased negative affect is also present, although not MDD-specific. However, blame attribution models (Abramson et al., 1978, Kinderman and Bentall, 1997) would suggest that memories involving blaming the self, relative to blaming others, might be relevant; an imbalance of self- and other-blaming feelings has recently been demonstrated in rMDD (Zahn et al., 2015a, Green et al., 2013b). There is also evidence that a self-blaming bias may be relevant in the autobiographical memory retrieval of people with MDD; an fMRI study (Green et al., 2012) reported a self-blame-selective functional decoupling of the hippocampus with the anterior temporal lobe in an rMDD group relative to an HC group. The hippocampus has a role in autobiographical memory retrieval (Gilboa et al., 2004), and the anterior temporal lobe in conceptual knowledge (Lambon Ralph, 2013), including knowledge for social concepts (Zahn et al., 2007, Zahn et al., 2009c); the authors suggested that the self-blame-selective decoupling of these two areas represented diminished differentiation between specific memories (Green et al., 2012). This model predicts that people with rMDD would retrieve less detail for self-blame related memories. To our knowledge, self-blame-related biases in memory have not been previously researched in the OGM literature. It is important to study any distinction between this and valence-related biases.

The Autobiographical Memory Test, a dominant method in this field, tests recall of associative memory for autobiographical information in a specific temporal and spatial context. However, performance on this test correlates with measures of executive function, independent of mood symptoms (Dalgleish et al., 2007).
Recognition memory tasks carry less executive load (Kopelman and Stanhope, 1998, Haist et al., 1992), so we designed a novel recognition task to probe associative memory for temporal and spatial context using manipulation of irrelevant contextual details in social action stimuli. This task was balanced across conditions to allow separate investigation of both valence- and blame-related biases, without the confounding effects of executive load. Episodic autobiographical and non-autobiographical memories have both been shown to depend on the same medial temporal lobe systems (Svoboda et al., 2006, Cabeza and Nyberg, 2000), so use of the latter will probe the neural circuitry of interest.

The task was completed by an rMDD and HC group to study vulnerability to depression rather than the state of depression (Bhagwagar and Cowen, 2008); the rMDD group also completed a longitudinal phase of the study to investigate predictive effects. History of ELS was also included as a factor to investigate its involvement in memory specificity.

We tested the alternative predictions of the self-blaming bias and the negative emotionality models of vulnerability to MDD on associative memory for temporal and situational context. The task design was balanced so as to allow the data to support either or both predictions. However, we favoured the hypothesis that the rMDD group would show self-blame-selective rather than negative emotion-selective changes in associative memory when compared to the HC group. Our more specific working hypothesis was that compared to the HC group, the rMDD group would show a reduced contextual memory for self-blame-related scenarios compared to scenarios related to blaming others. This was based on the assumption that reduced contextual memory would increase proneness to overgeneralisation. We also hypothesised that this self-blaming bias would be stronger in participants with ELS and participants who subsequently developed another episode of depression.

6.3 Method

6.3.1 Participants

Potential participants responded to advertisements, in both print and online media, for the UK Medical Research Council-funded project “Development of Cognitive and Imaging Biomarkers Predicting Risk of Self-Blaming Bias and Recurrence in Major Depression”. After receiving full information about the study, 707 participants
gave oral consent to an initial screening interview via telephone (see Supplemental Table 6.1). Suitable participants gave written informed consent and were assessed by a senior psychiatrist (RZ) and with the Structured Clinical Interview-I for DSM-IV (First et al., 2002). For inclusion in the rMDD group, participants had at least one major depressive episode (MDE) of at least two months duration, had been in remission for at least six months and were free from centrally-active medication (except hormonal contraceptives). They also had no current co-morbid or relevant past axis-I disorders. For the HC group, participants had no personal or first-degree family history of MDD. For full details of inclusion and exclusion criteria and recruitment procedures, see Chapter 2.1; this procedure is also documented in the Supplemental Materials of previous work (Zahn et al., 2015a).

Participants were reimbursed for their time and travel costs. This research study was approved by the South Manchester NHS Research Ethics Committee (reference number: 07/H1003/194).

As part of this larger study, 55 rMDD and 30 HC participants completed an associative memory for social actions task. Data from two rMDD participants were not included in analyses due to current depression at the time of task completion. This paper reports comparisons between three different groupings of the same participants. Firstly, a cross-sectional comparison of rMDD with HC. Secondly, groups were split into two subgroups: with (rMDD: n = 25, HC: n = 5) and without (rMDD: n = 28, HC: n = 24) the presence of ELS. This was defined as any of the following prior to the age of 18: separation from parents through death, divorce or adoption; threatened loss of parents through near death; threatened or actual physical or sexual abuse; witnessing violence between or towards parents. This was determined post-hoc from a semi-structured interview as part of the initial clinical assessment (conducted by KL or JG), which included questions about the participant’s parents’ relationship status and quality, incidences of serious illness, violence and abuse, and any other traumatic events. Binary categorisation (ELS or no ELS) was subsequently conducted from interview data by two independent raters (JG and CW), with high inter-rater reliability (κ = 0.947). Although not a validated method, all criteria for ELS were covered in the interview. There was an insufficient number (n = 5) of HC participants with such ELS, so this group was not included in the “ELS subgroup” analysis. ELS data was missing for one HC participant. Thirdly
and finally, rMDD participants were followed up for 14 months after the initial clinical assessment, enabling creation of three rMDD subgroups: those who remained in “Stable Remission” \((n = 24)\), those with a “Recurring Episode” \((n = 13)\) and an intermediate group \((n = 11)\) who developed significant symptoms but did not reach the threshold for an MDE. To be included in the intermediate group, participants had a Psychiatric Status Rating (Keller et al., 1987) of 4, or 3 if treatment was required. These are termed “prospective groups”. Five participants did not complete the follow-up phase of the study, and so are not included in the prospective analysis.

The two cross-sectional groups did not differ on years of age \((\text{rMDD: median 38, range 18-64, HC: median 27.5, range 20-64, } U = 694, p = 0.338)\), years of education \((\text{rMDD: median 17, range 12-22, HC: median 17, range 14-21.5, } U = 695, p = 0.339)\), or gender \((\text{rMDD: 39 females, HC: 19 females, } X^2 = 0.957, p = 0.328)\).

The Global Assessment of Functioning Scale (GAF) (First et al., 2002) showed that the HC group had higher levels of social and occupational functioning and lower symptom levels \((\text{rMDD: median 90, range 70-90, HC: median 90, range 80-90, } U = 531, p = 0.02)\). However, all participants had no more than mild symptoms or functioning problems. All participants also had Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery and Åsberg, 1979) scores below the threshold for depression \(<10\) points), and scores did not differ between groups \((\text{rMDD: median 0, range 0-6, HC: median 0, range 0-4, } U = 720.50, p = 0.375)\). See Supplemental Materials for details of subgroups.

**6.3.2 Associative memory for social actions task**

Task stimuli were developed from social scenarios generated by HCs (Green et al., 2013a). For full details, see Chapter 2.4.

Before starting, participants were informed that they were completing a memory task, but not which particular aspect of the stimuli they would be tested on. Participants were presented with 80 written statements describing a specific social action between themselves and their best friend. In each statement, the agent was either the participant (‘self-agency’, \(n = 40\)) or their best friend (‘other-agency’, \(n = 40\)). Identical statements were used in each agency condition save for the agency reversal and an irrelevant contextual detail (the time or location of the action).
Statements in each agency condition were either positive \((n = 20)\) or negative \((n = 20)\), forming four conditions: self-praise, other-praise, self-blame and other-blame, e.g. “At your party, Paul spilled wine on your hall carpet” (other-blame; Paul is the best friend). Number of words was balanced between conditions. Stimuli were presented for 6 seconds each in a random order using E-Prime 2 (http://www.pstnet.com/). After each sentence, participants rated its valence using a binary scale (good/bad).

Approximately 60 minutes later, participants were again presented with 80 stimuli, half of which had been shown before, the rest being foils. Foils were identical to a sentence shown previously, but with a contextual detail changed. The change was irrelevant to the meaning of the social action, such as the time or the place, e.g. “At your party, Paul spilled wine on your lounge carpet”. The number of foils was equal in each condition, as was the number of foils which were a time- or place-change. Each stimulus appeared for 6 seconds; after each stimulus, participants had 3 seconds to make a forced choice on whether or not that exact sentence had appeared earlier (yes/no). Responses outside this time window (<1% of all responses) were not recorded.

All responses were made using a designated key on a computer keyboard. One key for each response option was assigned to the index and middle fingers of the right hand (finger-to-response assignment was randomised across participants). Response time and accuracy were measured and the time interval between encoding and retrieval phases of the task (hereafter termed the ‘time interval’) was recorded in minutes.

**6.3.3 Data analysis**

For each condition within each participant, a speed-accuracy trade-off score was created using the following procedure.

The proportion of hits (correct identification of a previously seen sentence) and the proportion of false alarms (incorrect identification of a foil as previously seen) were calculated; these proportions were then transformed into \(z\)-scores using the NORMSINV function in Microsoft Excel. Missed responses were removed; overall, <1% of trials were missed, and no more than four responses were missed by a participant in any one condition. Where hit rate or false alarm rate was at ceiling or
floor level, these scores were adjusted by half a trial in the appropriate direction. This avoided creating an infinite \( z \)-score, whilst distinguishing the score from the next closest score (Durrant et al., 2013). Signal detection measure \( d' \) was then calculated by \( z \)-score (hits) – \( z \)-score (false alarms).

Mean response time was also calculated; where responses were missed, response time was set as the maximum response window (3 seconds). The speed-accuracy trade-off score was calculated by dividing mean \( d' \) by mean response time. A higher speed-accuracy trade-off score indicates high accuracy and fast response; conversely a lower score indicates low accuracy and slow response. These scores were then used to create composite scores to investigate self-other-blaming and positive-negative biases.

The average of scores from conditions related to blaming others relative to oneself (other-blame and self-praise) was subtracted from the average of scores from conditions related to blaming oneself relative to others (self-blame and other-praise); this gave an overall measure of self-blaming bias. A positive score indicates a bias towards remembering self-blame-related stimuli, and the higher this score, the greater the bias. Conversely, a negative score indicates a bias towards remembering other-blame-related stimuli.

The average of scores from negative conditions (self- and other-blame) was subtracted from the average of scores from positive conditions (self- and other-praise) to give an overall measure of positive valence bias. A positive score indicates a bias towards remembering positively-valenced stimuli, and the higher this score, the greater the bias. Conversely, a negative score indicates a bias towards remembering negatively-valenced stimuli.

Difference scores were created, as the condition differences (self vs. other, positive vs. negative) are the main variables of interest when studying biases; difference scores can also increase statistical power in the model (Jamieson, 2007).
6.4 Results

Table 6.1 Data summary table from the associative memory for social actions task averaged over conditions and groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Condition</th>
<th>Hits</th>
<th>Misses</th>
<th>False Alarms</th>
<th>Correct Rejections</th>
<th>d'</th>
<th>Beta Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>HC</td>
<td>Self-praise</td>
<td>6.73</td>
<td>3.27</td>
<td>3.43</td>
<td>6.57</td>
<td>0.96</td>
<td>1.09</td>
</tr>
<tr>
<td>HC</td>
<td>Self-blame</td>
<td>5.87</td>
<td>4.13</td>
<td>3.83</td>
<td>6.17</td>
<td>0.60</td>
<td>1.16</td>
</tr>
<tr>
<td>HC</td>
<td>Other-praise</td>
<td>7.03</td>
<td>2.97</td>
<td>3.63</td>
<td>6.37</td>
<td>0.98</td>
<td>1.01</td>
</tr>
<tr>
<td>HC</td>
<td>Other-blame</td>
<td>6.03</td>
<td>3.97</td>
<td>3.83</td>
<td>6.17</td>
<td>0.64</td>
<td>1.01</td>
</tr>
<tr>
<td>rMDD</td>
<td>Self-praise</td>
<td>6.92</td>
<td>3.08</td>
<td>3.60</td>
<td>6.40</td>
<td>0.97</td>
<td>1.01</td>
</tr>
<tr>
<td>rMDD</td>
<td>Self-blame</td>
<td>6.11</td>
<td>3.89</td>
<td>3.25</td>
<td>6.75</td>
<td>0.83</td>
<td>1.13</td>
</tr>
<tr>
<td>rMDD</td>
<td>Other-praise</td>
<td>7.19</td>
<td>2.81</td>
<td>3.81</td>
<td>6.19</td>
<td>1.01</td>
<td>1.05</td>
</tr>
<tr>
<td>rMDD</td>
<td>Other-blame</td>
<td>6.87</td>
<td>3.13</td>
<td>4.06</td>
<td>5.94</td>
<td>0.83</td>
<td>0.98</td>
</tr>
</tbody>
</table>

Table 6.2 Behavioural data for HC and rMDD groups Non-parametric tests were used where data were not normally distributed

<table>
<thead>
<tr>
<th>Variable</th>
<th>HC</th>
<th>rMDD</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-praise*</td>
<td>0.0016</td>
<td>0.0014</td>
<td>U = 754, p = 0.698</td>
</tr>
<tr>
<td>Self-blame*</td>
<td>0.0009</td>
<td>0.0012</td>
<td>U = 629, p = 0.116</td>
</tr>
<tr>
<td>Other-praise*</td>
<td>0.0015</td>
<td>0.0015</td>
<td>U = 725, p = 0.507</td>
</tr>
<tr>
<td>Other-blame*</td>
<td>0.0009</td>
<td>0.0011</td>
<td>U = 731.5, p = 0.547</td>
</tr>
<tr>
<td>BDI score</td>
<td>1.0 (0-6)</td>
<td>3.4 (0-17)</td>
<td>U = 448, p = 0.001</td>
</tr>
<tr>
<td>Number of past MDEs</td>
<td>-</td>
<td>3.6 (1-53)</td>
<td>-</td>
</tr>
<tr>
<td>FAS score</td>
<td>41.1 ± 10.8</td>
<td>43.6 ± 12.0</td>
<td>t = 0.944, p = 0.348</td>
</tr>
<tr>
<td>Trail-making score</td>
<td>26.5 (5.3-78.5)</td>
<td>23.0 (-1.7-64.0)</td>
<td>U = 738, p = 0.589</td>
</tr>
</tbody>
</table>

* Speed-accuracy trade-off scores created from d'/response time

Abbreviations: BDI, Beck Depression Inventory; HC, healthy control; MDE, major depressive episode, rMDD, remitted major depressive disorder

Data are summarised in Tables 6.1 and 6.2. All statistical analyses were conducted using SPSS20 (http://www.spss.com). Data fulfilled the standard assumptions for each statistical test unless otherwise stated.

For both the self-blaming and the valence measures, tests were conducted within the cross-sectional groups, the cross-sectional ELS subgroups and the prospective groups as follows: one-sample t-tests on each subgroup to detect significant biases from zero; univariate general linear models (GLM) with group variable as the fixed factor, the time interval as a covariate of no interest and the interaction term. Where
appropriate, results were confirmed by repeating tests with outlying values replaced with the mean ± 2.58 standard deviations.

6.4.1 Cross-sectional results
Statistical tests for differences within and between the cross-sectional groups and the same for the ELS subgroups.

6.4.1.1 Self-blaming measure
There were no biases from zero in any of the subgroups ($t \leq 1.029, p \geq 0.313$). The GLMs revealed no significant effects ($F \leq 1.050, p \geq 0.309$); see Table 6.3.

Table 6.3 Self-blaming measure

<table>
<thead>
<tr>
<th>Model</th>
<th>Main effect of group</th>
<th>Main effect of time interval</th>
<th>Interaction effect</th>
</tr>
</thead>
</table>
| Cross-sectional | $F[1,79] \leq 0.001, $  
$p = 0.994$  
$F[1,79] = 0.946, $  
$p = 0.334$  
$F[1,79] = 0.003, $  
$p = 0.957$ |                              |                    |
| ELS subgroups  | $F[2,71] = 0.126, $  
$p = 0.882$  
$F[1, 71] = 1.050, $  
$p = 0.309$  
$F[2, 71] = 0.102, $  
$p = 0.903$ |                              |                    |

6.4.1.2 Valence measure
A positive bias was found in the HC ($t[29] = 4.328, p \leq 0.001$) and rMDD groups ($t[52] = 2.319, p = 0.024$); results confirmed after outlier replacement (HC: unchanged; rMDD: $t[52] = 2.307, p = 0.025$). The GLM showed a main effect of group ($F[1, 79] = 4.033, p = 0.048$), but not of time interval ($F[1, 79] = 1.396, p = 0.241$). There was a trend for an effect of the interaction term ($F[1, 79] = 3.343, p = 0.071$). These results remained after outlier replacement (group: $F[1, 79] = 4.424, p = 0.039$; interaction term: $F[1, 79] = 3.651, p = 0.060$).

Additionally, both subgroups without a history of ELS showed positive biases (HC: $t[23] = 4.450, p \leq 0.001$; rMDD: $t[27] = 3.095, p = 0.005$); results confirmed after outlier replacement (HC: unchanged; rMDD: $t[27] = 3.232, p = 0.003$). Conversely, the rMDD group with ELS showed no bias from zero ($t[24] = 0.324, p = 0.749$). The GLM revealed a strong trend for a main effect of group ($F[2, 71] = 3.108, p = 0.051$) and a trend for an effect of the interaction term ($F[2, 71] = 2.497, p = 0.090$). There was no effect of time interval ($F[1, 71] = 0.807, p = 0.372$). These results remained
after outlier replacement (group: $F[2, 71] = 3.345, p = 0.041$; interaction term: $F[2, 71] = 2.688, p = 0.075$).

The HC group without ELS showed a significantly higher positive memory bias than the rMDD group with ELS ($p = 0.016$); result remained after outlier replacement ($p = 0.012$). The effect size for this was 0.74. There was no difference between any of the other groups ($p \geq 0.296$). These results are depicted in Figure 6.1. The effect sizes for the rMDD group without ELS were: 0.48 compared to the rMDD group with ELS and 0.24 compared to the HC group without ELS.

The positive valence bias score did not correlate with Beck Depresion Inventory scores (Beck et al., 1988) ($rho = -0.157, p = 0.157$), but correlated negatively with the number of past MDEs ($rho = -0.271, p = 0.050$); this means that as the number of MDEs increased, the positive bias reduced. The positive valence bias score did not correlate with measures of executive function: verbal fluency (as measured by the FAS score (Spreen and Strauss, 1998); $rho = -0.041, p = 0.714$); set-shifting (as measured by the trail-making test (Spreen and Strauss, 1998, Saraswat et al., 2006); $rho = 0.105, p = 0.347$).

![Figure 6.1 Means and standard error of the mean for the positive bias scores](image)

**Figure 6.1 Means and standard error of the mean for the positive bias scores** (average positive score – average negative score) are displayed by group. A positive score indicates a bias towards remembering self-blame-related stimuli, and the higher this score, the greater the bias. Positive bias score was significantly reduced in the rMDD with ELS compared to the HC group. No other group differences were seen (see main text for statistics).
6.4.2 Prospective results
ELS was not factored into these analyses, as the number of participants with and without ELS was not different across prospective groups ($X^2 = 0.334, p = 0.846$).

6.4.2.1 Self-blaming measure
There were no biases from zero in any of the prospective groups ($t \leq 0.944, p \geq 0.364$). The GLM revealed no significant effects of group ($F[3,70] = 0.777, p = 0.511$), time interval ($F[1,70] = 2.479, p = 0.120$) or interaction term ($F[3,70] = 0.876, p = 0.458$).

6.4.2.2 Valence measure
The Stable Remission group showed a trend for a positive bias ($t[23] = 1.942, p = 0.064$). No other groups showed a bias ($t \leq 1.555, p \geq 0.151$). The GLM showed no significant effects ($F \leq 1.134, p \geq 0.342$); see Table 6.4. However, the Recurring Episode group was non-normally distributed; a follow-up Kruskal-Wallis test confirmed there was no effect of group ($H[3] = 3.810, p = 0.283$). The effect size for the Recurring Episode compared to the Stable Remission group was 0.30, for Recurring Episode compared to HC was 0.62 and for Stable Remission compared to HC was 0.27.

Table 6.4 Valence measure

<table>
<thead>
<tr>
<th>Main effect of group</th>
<th>Main effect of time interval</th>
<th>Interaction effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>$F[3,70] = 1.134, p = 0.342$</td>
<td>$F[1,70] = 0.009, p = 0.926$</td>
<td>$F[3,70] = 0.958, p = 0.417$</td>
</tr>
</tbody>
</table>

6.5 Discussion
This study investigated blame- and valence-related biases in associative memory in rMDD and HC participants with and without ELS. The main hypothesis was that a reduction in specificity of self-blame-related memory recall would be seen in the rMDD group. Also, we predicted that the self-blaming bias would be stronger in the rMDD group compared to the HC group, particularly in the subgroup with ELS, and also in those who subsequently had another episode of depression.
Our results did not confirm the primary hypothesis, as no evidence of a self-blame-related memory bias was found in any of the groups or subgroups; self-blame-related scores also had no predictive effect. To our knowledge, self-blame-related biases have not been previously explored in the OGM literature, but given that an imbalance of self- and other-blaming feelings are a feature of rMDD (Zahn et al., 2015a, Green et al., 2013b), it was an area worthy of investigation. A self-blame-specific decoupling of the hippocampus with the anterior temporal lobe in rMDD participants (Green et al., 2012) was suggested as a correlate of reduced differentiation between self-blame-related memories; however the present task suggested this is not the case.

Conversely, a bias towards remembering contextual details of positive over negative stimuli was seen in both the HC and rMDD groups, and this bias was statistically stronger in the HC group. This fits with the general negative emotionality model, which states that positive affect is reduced in MDD (Watson et al., 1988). Furthermore, when factoring in ELS, only the rMDD subgroup with ELS lacked this positive bias. This group differed only from its polar opposite, the HC group with no ELS. This result relates to previous research; reduced specificity of autobiographical memories has previously been linked to both rMDD (Spinhoven et al., 2006) and ELS (Crane et al., 2014, Hitchcock et al., 2014, Burnside et al., 2004). Our findings extend this to specificity of social action memories presented in a personal context. Williams’ influential hypothesis (Williams, 1996) suggests that ELS leads to development of an overgeneral memory style which persists into adulthood, but it does not specify that there is a valence bias. However, a previous study (Aglan et al., 2010) found women with rMDD, particularly of adult-onset, and a history of childhood sexual abuse display higher OGM to positive than negative cues; other types of ELS did not yield significant effects. This supports our findings, which also suggest the effect generalises to both genders. Our results also collapsed across all types of ELS (only 6/25 had childhood sexual abuse) and included a small number of participants with juvenile-onset rMDD (7/25). Conversely, an evaluative review (Moore and Zoellner, 2007) found that ELS was not the primary factor in OGM, and that a PTSD or MDD diagnosis was more relevant, although they did not evaluate valence biases. Our results do not refute this, as it could be the interaction of MDD history and ELS that lead to the loss of positive memory bias seen here. The positive
bias score negatively correlates with the number of past MDEs. It is possible that ELS leads to initial development of an overgeneral memory style (Williams, 1996), and the subsequent experience of MDEs leads to cumulative reactivation of traumatic memories, and reinforces overgeneral memory with a specific loss of positive memory bias.

Unfortunately, as there were too few HC participants with ELS to include in the analysis, it is unknown if ELS irrespective of psychiatric history would produce a loss of positive memory bias. However, the HC and rMDD groups without ELS do not differ statistically, and so a history of MDD alone is not sufficient to significantly reduce the positive bias, as also seen by Aglan and colleagues (Aglan et al., 2010); ELS must play a significant role. Further research is also required to separate the effects of encoding and retrieval on this loss of positive contextual memory bias.

Importantly, unlike the commonly-used Autobiographical Memory Test (Dalgleish et al., 2007), the positive valence bias score did not correlate with measures of executive function. This indicates that this is a true measure of impaired access to associative memories rather than of general executive difficulties.

In terms of prediction, only the Stable Remission subgroup showed a trend towards a positive bias. However, group differences were not seen between the prospective rMDD subgroups, and the effect sizes were weak, so this positive bias was not predictive in this study. Low power may have been due to low sample size in the prospective rMDD subgroups; a larger sample size may yield predictive effects and should be investigated further in future studies. Overgeneralisation specific to positive memories has previously been found to be predictive of future depressive symptoms in early adolescent girls (Hipwell et al., 2011) and currently depressed adults (Brittlebank et al., 1993); our result suggests this may not be the case in a remitted adult population. However, other studies finding a valence bias to be predictive had follow-up periods of seven months (Brittlebank et al., 1993) and one year (Hipwell et al., 2011) compared to 14 months in the current study. A previous meta-analysis has indicated that shorter follow-up periods are associated with stronger predictive effects of OGM (Sumner et al., 2010); it is possible that the
positive bias would have shown stronger predictive effects with a follow-up period of less than a year.

In this study, we have defined ELS by experience of a fixed set of potentially stressful events in childhood, rather than by the response of the participant to that stressor. It has previously been suggested (Moore and Zoellner, 2007) that a traumatic response drives OGM, rather than experience of a stressful event per se. Although severity of response to each stressor was not assessed, all our participants were screened for history of PTSD. Two participants met PTSD criteria in adulthood, which was remitted at the time of study entry. Relevant analyses were repeated after removing these participants to confirm that their post-traumatic reactions did not drive any effects. Results were comparable without inclusion of their data (see Supplemental Materials). Therefore, this study would suggest that a post-traumatic response to a stressor is not necessary to see changes in OGM. A recent meta-analysis (Ono et al., 2015) supports this view; a consistent bias for recall of generalised memories to negative cues was found in those with trauma history, even without subsequent PTSD development. The direction of this result does not support our main study finding, but this is likely to be because results were collapsed across studies with childhood and adult trauma, and mildly- and never-depressed participants.

In summary, our findings demonstrated a loss of positive bias for associative memory in rMDD patients with a history of ELS. This was in contrast to both rMDD and HC groups without ELS, which showed statistically similar clear positive biases. These results suggest that it is the presence of ELS which drives the difference, although interaction with a history of MDD cannot be discounted. The negative association of the positive bias score with the number of past MDEs may indicate that it is the cumulative trauma of MDEs, combined with ELS, that leads to the selective loss of positive memory. Further work is also required in other clinical populations, such as PTSD, and also healthy populations to establish how ELS interacts with and contributes to associative memory biases in psychiatric disorders.
Supplemental Materials

Participant recruitment
707 participants gave oral consent to an initial screening interview via telephone. Full details of inclusion and exclusion criteria can be found in Chapter 2.1. Reasons for exclusion of participants from the associative memory for social actions task are detailed in Supplemental Table 6.1.

Participant characteristics

Cross-sectional ELS subgroups
The three cross-sectional ELS subgroups did not differ on years of age (HC without ELS: median 27.5, range 20-64, rMDD without ELS: median 39.5, range 20-63, rMDD with ELS: median 34, range 18-64, \( H = 1.733, p = 0.420 \)), years of education (HC without ELS: median 17.5, range 14-21.5, rMDD without ELS: median 17, range 12-21, rMDD with ELS: median 17, range 12-22, \( H = 2.602, p = 0.272 \)), or gender (HC without ELS: 16 females, rMDD without ELS: 21 females, rMDD with ELS: 18 females, \( X^2 = 0.446, p = 0.8 \)).

All participants had MADRS scores within the normal range, and scores did not differ between groups (HC without ELS: median 0, range 0-2, rMDD without ELS: median 0, range 0-6, rMDD with ELS: median 0, range 0-4, \( H = 2.408, p = 0.3 \)). GAF scores did differ between the groups (HC without ELS: median 90, range 81-90, rMDD without ELS: median 90, range 70-90, rMDD with ELS: median 90, range 75-90, \( H = 11.998, p = 0.02 \)). Follow-up Mann-Whitney tests showed no difference between the two rMDD subgroups (\( U = 307.5, p = 0.401 \)). The HC without ELS group differed from both rMDD subgroups (with ELS: \( U = 167, p = 0.01 \), without ELS: \( U = 219, p = 0.04 \)); this is expected given the cross-sectional groups differences shown in the main paper. All participants had no more than mild symptoms or functioning problems.

Prospective groups
The prospective groups did not differ on years of age (HC: median 27.5, range 20-64, Stable Remission: median 41, range 22-63, intermediate: median 38, range 28-58, Recurring Episode: median 38, range 18-64, \( H = 2.014, p = 0.569 \)), years of education (HC: median 17, range 14-21.5, Stable Remission: median 17.5, range 14-
### Supplemental Table 6.1 Exclusion reasons for volunteers prior to memory task

<table>
<thead>
<tr>
<th>Reason for exclusion</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Following telephone screening interview:</strong></td>
<td></td>
</tr>
<tr>
<td>Current antihypertensive medications or statins</td>
<td>20</td>
</tr>
<tr>
<td>Current antidepressant or other centrally active medications</td>
<td>52</td>
</tr>
<tr>
<td>Diabetes</td>
<td>4</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>5</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>3</td>
</tr>
<tr>
<td>Past cancer</td>
<td>7</td>
</tr>
<tr>
<td>Past stroke</td>
<td>1</td>
</tr>
<tr>
<td>Thyroid function problems</td>
<td>19</td>
</tr>
<tr>
<td>Vitamin D deficiency</td>
<td>1</td>
</tr>
<tr>
<td>Other psychiatric disorders than MDD</td>
<td>54</td>
</tr>
<tr>
<td>Substance or alcohol abuse</td>
<td>23</td>
</tr>
<tr>
<td>Other general medical condition</td>
<td>5</td>
</tr>
<tr>
<td>Family history of MDD/bipolar/schizophrenia (control group)</td>
<td>26</td>
</tr>
<tr>
<td>Excluded because of age-matching (control group)</td>
<td>3</td>
</tr>
<tr>
<td>Left-handed</td>
<td>20</td>
</tr>
<tr>
<td>MRI contraindications</td>
<td>77</td>
</tr>
<tr>
<td>Non-native English speaker</td>
<td>19</td>
</tr>
<tr>
<td>Out of age range</td>
<td>4</td>
</tr>
<tr>
<td>No reason recorded</td>
<td>5</td>
</tr>
<tr>
<td>Withdrawal after telephone screening interview</td>
<td>33</td>
</tr>
<tr>
<td>Not meeting full screening criteria for MDD</td>
<td>30</td>
</tr>
<tr>
<td>Had not been remitted from an episode for long enough</td>
<td>7</td>
</tr>
<tr>
<td>Fulfilled criteria for current MDD</td>
<td>13</td>
</tr>
<tr>
<td><strong>Total excluded after telephone screening interview</strong></td>
<td>431</td>
</tr>
<tr>
<td><strong>Following selection for initial assessment:</strong></td>
<td></td>
</tr>
<tr>
<td>Unable to schedule initial assessment</td>
<td>74</td>
</tr>
<tr>
<td>Fulfilled criteria for a bipolar disorder</td>
<td>6</td>
</tr>
<tr>
<td>Fulfilled criteria for current generalized anxiety disorder</td>
<td>1</td>
</tr>
<tr>
<td>Fulfilled criteria for current social anxiety disorder</td>
<td>7</td>
</tr>
<tr>
<td>MRI contraindications</td>
<td>1</td>
</tr>
<tr>
<td>Did not meet full criteria for MDD</td>
<td>5</td>
</tr>
<tr>
<td>Had not been remitted from an episode for long enough</td>
<td>3</td>
</tr>
<tr>
<td>Fulfilled criteria for past substance abuse</td>
<td>4</td>
</tr>
<tr>
<td>Probable personality disorder</td>
<td>2</td>
</tr>
<tr>
<td>Showed residual symptoms of post-traumatic stress disorder</td>
<td>3</td>
</tr>
<tr>
<td>Fulfilled criteria for current adjustment disorder</td>
<td>1</td>
</tr>
<tr>
<td>Fulfilled criteria for current MDD</td>
<td>1</td>
</tr>
<tr>
<td>Non-native English speaker</td>
<td>1</td>
</tr>
<tr>
<td>Fulfilled criteria for a past MDE that lasted for less than two months (control group)</td>
<td>1</td>
</tr>
<tr>
<td>Past depressive episode that did not fulfill criteria for past MDE (control group)</td>
<td>1</td>
</tr>
<tr>
<td>Probable or definite positive first degree family history of MDD (control group)</td>
<td>4</td>
</tr>
<tr>
<td>Withdrawal after the first assessment</td>
<td>1</td>
</tr>
<tr>
<td>Enrolled onto study prior to memory task development</td>
<td>38</td>
</tr>
<tr>
<td>Unable to schedule memory task session</td>
<td>27</td>
</tr>
<tr>
<td>Excluded because of age-matching for memory task (control group)</td>
<td>6</td>
</tr>
<tr>
<td>Ineligible for other tasks done in same session as memory task</td>
<td>4</td>
</tr>
<tr>
<td><strong>Total excluded from this session after selection for initial assessment</strong></td>
<td>191</td>
</tr>
</tbody>
</table>

707 participants consented to the telephone screening interview. After exclusions, 85 participants (55 rMDD, 30 HC) completed the associative memory for social actions task. Abbreviations: HC, healthy control; (r)MDD, (remitted) major depressive disorder; MDE, major depressive episode.
22, intermediate: median 18, range 12-21, *Recurring Episode*: median 17, range 12-
18, \( H = 4.657, p = 0.199 \) or gender (HC: 19 females, *Stable Remission*: 18 females, 
intermediate: 10 females, *Recurring Episode*: 7 females, \( X^2 = 4.736, p = 0.192 \)).

All participants had MADRS scores within the normal range, and scores did not
differ between groups (HC: median 0, range 0-4, *Stable Remission*: median 0, range 
0-4, intermediate: median 0, range 0-2, *Recurring Episode*: median 0, range 0-6, \( H = 
1.654, p = 0.647 \)). GAF scores did differ between the groups (HC: median 90, range 
80-90, *Stable Remission*: median 90, range 75-90, intermediate: median 90, range 
80-90, *Recurring Episode*: median 86, range 70-90, \( H = 10.975, p = 0.012 \)). A 
follow-up Kruskal-Wallis test revealed no significant difference between the three 
rMDD subgroups (\( H = 2.005, p = 0.367 \)).

**Supplemental results**

Two participants had an adulthood diagnosis of PTSD, which was remitted at the 
time of testing. Both these participants were in the rMDD without ELS subgroup and 
the intermediate prospective group. All relevant analyses were repeated with these 
participants removed, and results were comparable to those reported in the main text.

**Cross-sectional results**

*Self-blaming measure*

There were no biases from zero in any of the subgroups (\( t \leq 0.812, p \geq 0.425 \)). The 
GLMs revealed no significant effects (\( F \leq 0.738, p \geq 0.393 \)); see Supplemental Table 
6.2.

**Supplemental Table 6.2 Self-blaming measure** No group differences were seen for 
the self-blaming bias

<table>
<thead>
<tr>
<th>Model</th>
<th>Main effect of group</th>
<th>Main effect of time interval</th>
<th>Interaction effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cross-sectional</td>
<td>( F[1,77] = 0.006 ), ( p = 0.938 )</td>
<td>( F[1,77] = 0.738 ), ( p = 0.393 )</td>
<td>( F[1,77] = 0.002 ), ( p = 0.968 )</td>
</tr>
<tr>
<td>ELS subgroups</td>
<td>( F[2,69] = 0.185 ), ( p = 0.832 )</td>
<td>( F[1, 69] = 0.700 ), ( p = 0.406 )</td>
<td>( F[2, 69] = 0.157 ), ( p = 0.855 )</td>
</tr>
</tbody>
</table>

*Valence measure*

A positive bias was found in the rMDD group (\( t[50] = 2.149, p = 0.036 \)). The GLM 
showed a trend for an effect of group (\( F[1,77] = 3.576, p = 0.062 \) and for the
interaction term ($F[1,77] = 2.900, p = 0.093$). There was no main effect of time interval ($F[1,77] = 1.573, p = 0.214$).

A positive bias was also found in the rMDD subgroup without ELS ($t[25] = 2.870, p = 0.008$). The GLM revealed a main effect of group ($F[2,69] = 3.129, p = 0.050$) and a trend for an effect of the interaction term ($F[2, 69] = 2.522, p = 0.088$). There was no main effect of time interval ($F[2,69] = 1.058, p = 0.307$). The rMDD group without ELS did not differ from either of the other ELS subgroups ($p \geq 0.408$).

**Prospective results**

*Self-blaming measure*

There was no bias from zero in the intermediate subgroup ($t[8] = 0.519, p = 0.618$). The GLM revealed no significant effects of group ($F[3, 68] = 0.748, p = 0.527$), time interval ($F[1, 68] = 2.294, p = 0.135$) or interaction term ($F[3, 68] = 0.840, p = 0.477$).

*Valence measure*

There was no bias from zero in the intermediate subgroup ($t[8] = 1.134, p = 0.289$); data were not normally distributed but a follow-up one-sample Wilcoxon signed rank test confirmed the result ($p = 0.110$). The GLM showed no significant effects of group ($F[3, 68] = 1.058, p = 0.373$), time interval ($F[1, 68] = 0.020, p = 0.887$) or interaction term ($F[3, 68] = 0.872, p = 0.460$). The intermediate and *Recurring Episode* groups were not normally distributed; a follow-up Kruskal-Wallis test confirmed there was no effect of group ($H[3] = 3.789, p = 0.285$).
References (Chapter 6)


Chapter 7: General Discussion

7.1 Purpose
The overarching aim of this thesis was to contribute to the understanding of major depressive disorder (MDD) vulnerability through the use of electroencephalography (EEG) and neuropsychological testing. Studies were designed to contribute to an established neural model of moral cognition, the event-feature-emotion complex (EFEC) model; this model hypothesises that moral emotions are brought about through the integration of fronto-temporo-limbic regions (Moll et al., 2005). Components of this model are known to be disrupted in remitted MDD (rMDD) (Green et al., 2012, Pulcu et al., 2014b, Lythe et al., in press) indicating the involvement of this network in depression vulnerability. A commonly used task in this literature is the value-related moral sentiment task (VMST)\(^\text{12}\) (Green et al., 2012, Pulcu et al., 2014a, Green et al., 2010, Zahn et al., 2009c, Lythe et al., in press), although so far this has only been used with functional magnetic resonance imaging (fMRI). EEG has a much higher temporal resolution than fMRI (Luck, 2014), so allows exploration of the temporal dynamics of the EFEC model. In addition, fMRI carries a high cost (Luck, 2014), so in addition to increasing understanding of the model, this thesis sought to evaluate the use of the VMST with EEG, a more cost-effective method (Luck, 2014).

In order to study vulnerability to depression, a cohort of rMDD participants was recruited, along with a matched healthy control (HC) group with no personal or family history of MDD. This allowed comparison of a high- and low-risk group to study vulnerability to future depression, without the confounding effects of differences in current mood state. rMDD participants also completed a 14-month follow-up period, during which symptoms were assessed at intervals to establish “Stable Remission” and “Recurring Episode” subgroups; this allowed study variables to be evaluated for their predictive effects on future major depressive episodes (MDEs).

\(^{12}\) The VMST is a social action judgement task designed to explore neurocognitive correlates of moral emotions associated with blaming the self and others (see Section 2.2 for more detail)
7.2 Summary of results

Chapter 3 investigated self-blame-selective effects in the theta and alpha bands, which are known to show changes at rest (Olbrich and Arns, 2013). No group effects were detected in the alpha band, but the rMDD group showed a self-blame-selective sustained increase in theta power, which was not present in the HC group. A composite score representing self-blame-selective theta over time correlated with fMRI activity in the right anterior dorsolateral prefrontal cortex (dLPFC). This was interpreted as altered temporal dynamics of the theta rhythms contributing to dysfunctional integration of contextual information in the dLPFC. This may contribute to the overgeneralisation of self-blaming emotions, a common feature of MDD (First et al., 2002).

Previous work has shown self-blame-selective functional disconnections within regions of the EFEC model in rMDD relative to HCs (Green et al., 2012); in particular, an anterior temporal lobe (ATL)-subgenual cingulate (sgACC) decoupling was thought to represent the overgeneralised self-blame (Green et al., 2012) experienced in MDD (First et al., 2002). In Chapter 4, analogous functional disconnections were investigated using EEG. However, no group differences in functional coupling between regions in the EFEC model were found in the psychophysiological interaction (PPI) analysis. Instead, an other-blame-specific reduced left dLPFC activation was found in the rMDD group relative to the HC group. The left dLPFC in particular has previously been associated with anger (van Honk et al., 2002, Harmon-Jones and Allen, 1998, Zahn et al., 2009c), but its activation did not correlate with the frequency of other-blaming emotions experienced during the task. An alternative suggestion is that reduced activation may alter the quality of other-blaming feelings, which cannot be assessed with a simple measure like the frequency of experiencing an emotion. Further work with more detailed ratings is required to confirm this.

Chapter 5 aimed to establish whether self-blame related EEG source signals correlated with equivalent fMRI source signals, in order to evaluate the use of EEG in lieu of fMRI in future studies. However, no correlation was demonstrated in our time window of interest.
Previous research has also found a self-blame-selective decoupling between the ATL and the hippocampus, which was thought to reflect diminished differentiation between specific memories (Green et al., 2012); overgeneralisation of autobiographical memories is a known feature of MDD (Williams, 2006). In Chapter 6, evidence for self-blame-specific overgeneralisation of associative memory was sought in order to further understand the previous imaging findings (Green et al., 2012). No self-blaming biases were detected, however a loss of positive bias in associative memory was found in rMDD participants with a history of early life stress (ELS), relative to both rMDD and HC groups without ELS. The negative correlation of the positive bias score with the number of past MDEs may indicate that it is the cumulative trauma of MDEs, combined with ELS, that leads to the selective loss of positive memory.

None of the outcome measures differed between both the Stable Remission and Recurring Episode subgroups, and these subgroups and the HC group, meaning no predictive markers for recurrence risk were found.

### 7.3 Theoretical and clinical implications

#### 7.3.1 EFEC model

The EFEC model states that the integration of fronto-temporo-limbic regions brings about the experience of moral emotions of all valences and agencies (e.g. guilt [negative, self-agency], anger [negative, other-agency], pride [positive, self-agency], gratitude [positive, other-agency]) (Moll et al., 2005). Given that elevated self-blame is seen in rMDD (Ghatavi et al., 2002), it is not surprising that there is evidence for self-blame-selective disruption within this network in rMDD (Green et al., 2012, Lythe et al., in press). Altered self-blame-selective theta in rMDD (Chapter 3) provides additional support for disrupted neural synchrony in rMDD, as theta is thought to have a role in synchronisation of distributed brain areas (O’Neill et al., 2013, Klimesch, 1999, Jones and Wilson, 2005). This result is consistent with the general role of integration in the EFEC model (Moll et al., 2005), but the effects were not directly investigated at the source level, so cannot provide specific support for the EFEC model. However, elevated theta is consistently found in ventromedial and frontal regions in current depression using resting-state EEG (Arns et al., 2015, Jaworska et al., 2012, Korb et al., 2008). It could be argued that this reflects ongoing
self-blaming processes, and elevated theta seen in Chapter 3 would also localise to these areas; further analysis is clearly required to confirm this speculation.

An important region in this thesis was the dlPFC; the EEG results (Chapters 3 & 4) highlight the importance of the dlPFC in self- and other-blaming biases. There is prior evidence for the importance of the right dlPFC in self-blame; its self-blame-selective decoupling from the ATL was associated with non-adaptive conceptual-emotional integration (i.e. higher interdependence of emotional intensity and ability to differentiate between social concepts (Green et al., 2013a)). The results of Chapter 3 provide support for this; aberrant sustained theta, which also correlated with reduced right dlPFC fMRI activity, was seen in the rMDD group. This could represent reduced ATL-dlPFC coupling, given that theta is involved in temporal synchrony (Jones and Wilson, 2005, Klimesch, 1999, O'Neill et al., 2013); localisation of the EEG theta signal is needed to confirm this, as discussed above. Activation of the dlPFC, particularly on the left side, has also been linked to other-blaming emotions (van Honk et al., 2002, Harmon-Jones and Allen, 1998, Zahn et al., 2009c). Although reduced left dlPFC activity was seen in the rMDD group during the other-blame condition (Chapter 4), this did not correlate with the frequency of other-blame experiences. Instead, reduced activation may represent an alteration of the quality of other-blaming feelings, which cannot be assessed with a simple measure like the frequency of other-blame experiences. Whatever the interpretation of the findings in Chapters 3 & 4, increased activation of the dlPFC on either side appears to be adaptive, as the HC groups show higher activation. The results in this thesis confirm that the dlPFC is an important component of the moral cognition network.

7.3.2 EEG
Disruption within the EFEC model in rMDD had previously only been demonstrated with one imaging technique: fMRI. This thesis shows that self- and other-blaming biases are also detectable using the VMST in EEG (Chapters 3 & 4). Additionally, despite the negative results, Chapter 4 demonstrates that a PPI analysis of the EEG VMST task is possible using source analysis on single trial data. This has implications for future research and clinical translation; compared with fMRI, EEG is a much more cost effective method (Luck, 2014), which is also more widely
available (Gabriel et al., 2015) and also associated with fewer risks (Wager et al., 2007).

Integration of the different brain regions involved in the EFEC model is important to create “gestalt experiences”; the timing of the integration is therefore key (Moll et al., 2005). An effect in the temporal domain was demonstrated across a timeframe of 600 milliseconds (Chapter 3), highlighting the benefits of using a technique such as EEG with a temporal resolution that better reflects the speed of neural activity (Luck, 2014); such temporal information could never be obtained from using fMRI, as the temporal resolution is poorer by several orders of magnitude (Luck, 2014). There is more potential to understand the temporal dynamics of the EFEC model using EEG. However, the lack of EEG-fMRI correlation (Chapter 5) indicates that the results in this thesis are not directly comparable to previous work in fMRI (Green et al., 2012, Lythe et al., in press). Understanding this discrepancy would enable the temporal and spatial benefits of both techniques to be used in conjunction.

7.3.3 Memory
The findings of a loss of positive memory bias specific to those with rMDD and ELS, but which correlates with the number of past MDEs (Chapter 6) indicates an interaction between depression history and ELS in the overgeneralisation of positive memories. The direction of the valence bias is in keeping with the existing literature in rMDD (Gupta and Kar, 2012, Park et al., 2002). However, as the HC and rMDD groups without ELS did not differ, it is clear that a history of MDD alone is not sufficient to significantly reduce the positive bias. This adds to the growing body of literature highlighting the importance of ELS in memory overgeneralisation, both as an overall feature of memory (Burnside et al., 2004, Crane et al., 2014, Hitchcock et al., 2014) and to positive memories specifically (Aglan et al., 2010). It also emphasises the potential consequences of not including ELS history as a factor in studies of this nature.

A widely adopted task within the MDD and memory literature is the Autobiographical Memory Test (Liu et al., 2013, Moore and Zoellner, 2007); participants are timed until they produce a specific autobiographical memory in response to a cue word (e.g. “happy” or “lonely”; (Williams and Scott, 1988)). However, this task has been shown to correlate with measures of executive function
(Dalgleish et al., 2007). This brings into question whether the Autobiographical Memory Task is a specific test of impaired access to autobiographical memories (which can be thought of as a form of associative memory (Howe, 2015)), or of general executive difficulties, a known feature of MDD (Snyder, 2013). The newly developed associative memory for social actions task does not correlate with measures of executive function (Chapter 6), so represents a much more specific test of associative memory function. Although consistency of methodology within a body of literature is an advantage, as it allows for easier comparison of results between studies, this highlights the necessity for properly controlled tasks to ensure results can be interpreted in the intended way.

7.4 Limitations and future directions

7.4.1 General study design
An important limitation of the overall study design was the inability to distinguish primary from secondary vulnerability to developing depression within the cross-sectional results; primary vulnerability exists before the first MDE and secondary vulnerability is the added risk of developing another MDE as a result of a previous one (Solomon et al., 2000), including so-called scarring effects (Burcusa and Iacono, 2007). To address this limitation within the cross-sectional results, key outcome measures were correlated with the number of previous MDEs to establish whether the result was associated with scarring effects or with primary vulnerability. However, in order to distinguish vulnerability type conclusively, a study needs to recruit participants at high risk of MDD, prior to their first episode; an example of such participants are those with a first-degree family history of MDD but without a personal history of MDD (Young et al., 2013). This was not done in this study, as its primary aim was to investigate the prediction of recurrence within an rMDD population. However, ultimately all of the group differences came from the cross-sectional analyses (Chapters 3, 4 & 6), and so it would be interesting to investigate how a group of at-risk but never-depressed participants would compare on the same tasks.

Great care was taken during participant recruitment to only include those who met the carefully selected inclusion/exclusion criteria, including fulfilling past MDE criteria (see Section 2.1). However, MDD is a heterogeneous disorder, with only five
of a possible nine symptoms required for a diagnosis; this means that two participants in the study might only share a single symptom (First et al., 2002). Although the majority of the cohort did report experiencing excessive self-blame during their MDEs, almost 20% did not (Zahn et al., 2015b). Exploring self-blame-selective effects in those that did not experience them may weaken any differences between rMDD and HC groups. Indeed, subtypes of MDD with differing symptoms have been shown to have differences in resting state fMRI connectivity networks (Workman et al., under review). Although this would add an additional challenge to recruitment, studying only those with a history of excessive self-blame would improve the specificity of study. Additionally, it would mean any clinical translations are more relevant to the subgroup of MDD patients for whom they are intended.

7.4.2 EEG
An issue of using a task adapted from fMRI for use with EEG is that EEG requires a higher number of trials to reach an acceptable level of signal-to-noise ratio (Yesilyurt et al., 2010). To increase the number of trials available for analysis, self- and other-blame were contrasted rather than their subordinate specific feelings such as guilt, indignation and shame, which were used in previous studies (Green et al., 2012, Pulcu et al., 2014a). However, it is evident from the effect size of the theta interaction (Chapter 3) that more power was required. As groups were inevitably smaller in the prospective part of the study, the power issue may also have contributed to the lack of predictive group effects (Chapters 3 & 4). More power could be achieved through increasing the number of participants, but this is not an ideal solution given that the ultimate aim was to identify a biomarker that would have use at an individual level. An alternate solution would be to ask participants to make unpleasantness ratings on the VMST stimuli prior to the EEG session, and then tailor the task stimuli to their ratings (i.e. only show stimuli rated as highly intensely unpleasant). This would allow fewer trials to be discarded, but importantly would not make the recording session any longer. This technique should be adopted by future studies using the VMST with EEG.

In order to optimise the source localisation, priors from the parallel fMRI study were used. The priors were taken from blood-oxygen-level dependent data of 37 HC and 69 rMDD participants using the combination of two contrasts (self-blame > fixation
and other-blame > fixation). This particular combination was used to ensure that the priors represented regions associated with both conditions of interest and both groups. Although it was not possible to use different priors for the different groups and conditions, as this would cause a bias when testing for differences, it is possible that any such differences were reduced by this approach; group differences in source activation and the PPI analyses (Chapter 4) may have been seen without the use of priors. Changes in the sources may also have altered findings of the EEG source-fMRI correlation (Chapter 5). However, it was always the intention to combine fMRI information with the EEG data in order to benefit from the combined spatial and temporal benefits of both techniques (Luck, 2014). Additionally, priors are only included in the source solution if they reduce the error in the solution (Litvak et al., 2011), so not using priors would most likely have reduced the accuracy of the sources. In future studies, it may be worth conducting parallel models with and without priors and comparing the accuracy of the model fit; if this does not differ greatly, analysing the model without priors should be considered.

An additional level of uncertainty was added into the source reconstruction for the PPI analysis (Chapter 4), as the sources were identified at the single-trial level rather than the condition average-level. Any error in the location of sources would also have been amplified in the PPI analysis itself, as this method measures correlation of the activity between two sources. This is potentially a major factor in the lack of PPI findings in this study (Chapter 4). However, lack of findings could also be due to the selection of seed region; PPI is unidirectional, only identifying regions whose signal timecourse can be predicted by that of the seed region (Friston et al., 1997). Although the ATL has been successfully used as a seed region in previous PPI analyses (Green et al., 2012, Lythe et al., in press), so was selected with good reason, there are other regions of the EFEC model (Moll et al., 2005) which could have been used. For example, a recent fMRI resting state analysis in rMDD used the sgACC as a seed region (Workman et al., under review). However, it is worth noting that the sgACC is located far from the cortical surface. Sources nearer the cortical surface inevitably contribute more to the EEG signal than deep sources (Wager et al., 2007), so activity from this area may have been difficult to reliably detect, and thus may not have made an ideal seed region in a PPI analysis.
The theta power interaction score showed correlation with right dorsolateral prefrontal cortex fMRI measures (Chapter 3). As previously discussed (Section 7.3.1), this is likely to represent temporal synchrony of areas involved in the EFEC model. However, it is possible to localise the sources of theta power itself (Arns et al., 2015, Jaworska et al., 2012, Korb et al., 2008). Taking into consideration issues with source localisation discussed above, localising the theta power over time would be an informative next step in understanding how theta contributes to the EFEC network.

An advantage of EEG is its high temporal resolution (Luck, 2014). Group differences in signal over time were demonstrable (Chapter 3). However, for practical reasons, a single time window had to be selected for the majority of the EEG analyses (Chapters 4 & 5). This time window was selected as being most likely to capture semantic processing (see Section 2.3.3), and therefore where group differences were expected. However, all future analyses should consider different time points in order to utilise the full potential of EEG.

The lack of EEG-fMRI correlation (Chapter 5) makes the EEG results (Chapters 3 & 4) difficult to directly compare to previous work in fMRI (Green et al., 2012, Lythe et al., in press). Simultaneous EEG-fMRI acquisition could improve understanding of how the two signals correlate. Additionally, collecting all data within one session reduces any variation from external factors such as current mood state. However, this would be an initial step rather than a long-term solution, as simultaneous acquisition is not a well suited to clinical translation.

7.4.3 Memory

The association of reduction in positive bias and higher number of past MDEs suggests a role of depression history in the findings (Chapter 6). However, this correlation was moderate (Field, 2009), and so recruitment of an HC group with ELS would be required in order to make firmer conclusions regarding the role of depression history on associative memory biases. This group was not specifically recruited, as investigating the effects of ELS was not the primary aim of the overall study. The fact that our cohort included so few HC participants with ELS reflects the naturalistic recruitment process of the overall study, as ELS is a risk factor for MDD (Chapman et al., 2004).
It would also be interesting to use the associative memory for social actions task in other psychiatric populations. In particular, post-traumatic stress disorder (PTSD) would be of interest given the link to ELS that has been demonstrated (Chapter 6). It has also been noted that traumatic events in adulthood can result in overgeneralisation of memory (Moore and Zoellner, 2007). In the present study, there were insufficient participants with PTSD diagnosed in adulthood to investigate effects of later life trauma, although removing these did not affect the main study findings (Chapter 6: Supplementary Materials); investigation of the timing of stressful life events on memory biases in both MDD and PTSD would be interesting future work.

A potential criticism of the associative memory for social actions task is that, in contrast to the commonly-used Autobiographical Memory Test, its stimuli were not autobiographical. However, through inclusion of their name and their best friend’s name, and also by direct instruction, participants were encouraged to assess stimuli as if they were personal experiences. This was thought to provide a good approximation of how true autobiographical memories are processed, and additionally allowed for good control of factors such as working memory load. To confirm that the results apply to autobiographical memories, it may be possible to adapt the task to be used with real-life autobiographical memories produced by participants and modified foils created by experimenters. This would be more labour-intensive, especially as stimuli would require balancing for working memory load (i.e. word count) across conditions for each individual participant. Additionally, if participants were asked in advance to report some specific autobiographical memories, they may be more likely to remember them in detail when subsequently tested, resulting in ceiling effects.

7.5 Final conclusions
In summary, the evidence for the role of self-blame in rMDD was not consistent. Although blame-related neural responses were seen, the results with the strongest effect size were valence-related; the same data showed no significant blame-related effects. Additionally, unfortunately no electrophysiological or neurocognitive predictive markers of recurrence risk were found. However, interesting effects were found in the cross-sectional analyses.
A novel memory task demonstrated a loss of positive memory bias which was specific to members of the rMDD group with ELS. This memory task has an advantage over the existing dominant task in the literature in that it does not correlate with measures of executive function; it represents a more specific test of associative memory which could be adopted by the field. Additionally, this result emphasises the importance of including ELS as a factor in studies of associative memory biases.

No direct evidence was found to support the EFEC model above other moral cognitive neuroscience models of MDD. However, EEG was validated as a technique for detecting self- and other-blame-specific neural correlates of vulnerability to depression, most notably in the temporal domain; this is an advantage of EEG over previously used techniques. This work sets the stage for exploration of the EFEC model using a technique with the potential to capture the temporal dynamics involved in the moral cognition network.
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